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Wednesday
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Pesticides and Pests
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FEDERAL REGISTER Published daily, Monday through Friday, (not published on Saturdays, Sundays, or on official holidays), by the Office of the Federal Register, National Archives and Records Service, General Services Administration, Washington, DC 20408, under the Federal Register Act (49 Stat. 500, as amended; 44 U.S.C. Ch. 15) and the regulations of the Administrative Committee of the Federal Register (1 CFR Ch. I). Distribution is made only by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.

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Questions and requests for specific information may be directed to the telephone numbers listed under INFORMATION AND ASSISTANCE in the READER AIDS section of this issue.

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Animal and Plant Health Inspection Service

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Presidential Documents

Title 3—

The President

Executive Order 12499 of January 18, 1985

President's Blue Ribbon Task Group on Nuclear Weapons Program Management

By the authority vested in me as President by the Constitution and laws of the United States of America, and in order to establish, in accordance with the provisions of Section 1632 of the Department of Defense Authorization Act, 1985 (Public Law 98–525) ("the Act"), and of the Federal Advisory Committee Act, as amended (5 U.S.C. App. I), a Blue Ribbon Task Group on Nuclear Weapons Program Management, it is hereby ordered as follows:

Section 1. *Establishment.* (a) There is established the President's Blue Ribbon Task Group on Nuclear Weapons Program Management. The Task Group shall consist of seven members qualified for service by reasons of experience and education. The President shall appoint three members and shall designate one of those members to act as chairman of the Task Group. The chairman and ranking minority members of the Committees on Armed Services of the Senate and House of Representatives will each appoint one member.

(b) None of the members of the Task Group may be an employee of the Department of Defense or the Department of Energy.

Sec. 2. *Functions.* (a) The Task Group shall examine the procedures used by the Department of Defense and the Department of Energy in establishing requirements for, and in providing resources for, the research, development, testing, production, surveillance, and retirement of nuclear weapons and shall recommend any needed change in such procedures.

(b) The Task Group shall report to the President and the Committees on Armed Services of the Senate and the House of Representatives as specified in its charter but not later than July 15, 1985. The Task Group's report shall contain recommendations in the areas specified in Section 1632(e) of the Act.

Sec. 3. *Administration.* (a) The heads of Executive agencies shall, to the extent permitted by law, provide the Task Group such information as it may require for purposes of carrying out its functions.

(b) Members of the Task Group shall serve without compensation for their work on the Task Group. To the extent funds are available therefore, all members of the Task Group performing duties away from their home or regular place of business, or designated post of duty, may be allowed travel expenses, as authorized by law, including per diem in lieu of subsistence for persons serving intermittently in the government service, as provided under 5 U.S.C. 5701–5707.

(c) The Secretary of Defense shall provide the Task Group with such administrative services, facilities, staff, and other support services as may be necessary. Any expenses of the Task Group shall be paid from such funds as may be available to the Secretary of Defense.

Sec. 4. *General.* (a) Notwithstanding any other Executive order, the functions of the President under the Federal Advisory Committee act, as amended, except that of reporting to the Congress, which are applicable to the Task Group, shall be performed by the Secretary of Defense, in accordance with guidelines established by the Administrator of General Services.

(b) The Task Group shall terminate on September 30, 1985, unless its existence is sooner extended in accordance with the Federal Advisory Committee Act.

Ronald Reagan

THE WHITE HOUSE,
January 18, 1985.

[FR Doc. 85-1901
Filed 1-22-85; 10:53 am]
Billing code 3195-01-M

Rules and Regulations

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This section of the FEDERAL REGISTER contains regulatory documents having general applicability and legal effect, most of which are keyed to and codified in the Code of Federal Regulations, which is published under 50 titles pursuant to 44 U.S.C. 1510.
The Code of Federal Regulations is sold by the Superintendent of Documents. Prices of new books are listed in the first FEDERAL REGISTER issue of each week.

DEPARTMENT OF AGRICULTURE

Office of the Secretary

7 CFR Part 17

Financing of Commercial Sales of Agricultural Commodities

AGENCY: Foreign Agricultural Service, USDA.

ACTION: Interim rule.

SUMMARY: This interim rule amends the regulations applicable to the financing of the sale and exportation of agricultural commodities pursuant to Title I of the Agricultural Trade Development and Assistance Act of 1954, as amended (Pub. L. 480, 83rd Cong.). These regulations appear at Part 17 of Title 7 of the Code of Federal Regulations. The amendment provides that Commodity Credit Corporation may finance ocean freight charges on foreign flag vessels for the carriage of commodities purchased under Title I, Pub. L. 480 program.

DATES: Effective Date: January 23, 1985. Comments on this interim rule must be received on or before March 15, 1985.

ADDRESS: Comments should be submitted to: Melvin E. Sims, General Sales Manager, Foreign Agricultural Service, Room 4073–S, U.S. Department of Agriculture, Washington, D.C. 20250. Comments available for public inspection during business hours 8:30 a.m. to 5:00 p.m. Monday through Friday; Room 4549 South Building, U.S. Department of Agriculture, Washington, D.C. 20250.

FOR FURTHER INFORMATION CONTACT: Donald R. Pickett, Acting Director, Pub. L. 480 Operations Divisions, Export Credits, Foreign Agricultural Service, U.S. Department of Agriculture, Washington, D.C. 20250. Telephone: (202) 447–6711.

SUPPLEMENTARY INFORMATION: This action has been reviewed under USDA procedures established in accordance with Executive Order 12291 and Secretary's Memorandum No. 1512–1 and has been classified "not major." It has been determined that this rule will not result in an annual effect on the economy of $100 million or more; will not cause a major increase in costs to consumers, individual industries, Federal, State or local government agencies or geographic regions; and will not have an adverse effect on competition, employment, investment, productivity, innovation, or the ability of U.S. based enterprises to compete with foreign based enterprises in domestic or export markets.

It has been determined that the Regulatory Flexibility Act is not applicable to this rule since the rule involves foreign affairs functions of the United States and therefore neither 5 U.S.C. 553 nor any other provision of law requires publication of a notice of proposed rule making with respect to the subject matter of this rule.

Section 102 of the Agricultural Trade Development and Assistance Act of 1954, as amended ("the Act") authorizes the Commodity Credit Corporation (CCC) to finance the sale and exportation of agricultural commodities purchased by friendly countries under the authority of Title I of the Act.

The regulations governing this program appear at 7 CFR Part 17. Currently these regulations only provide for financing ocean freight applicable to U.S.-flag vessels. Financing any part of the ocean freight on foreign flag vessels is specifically prohibited. As a matter of policy, financing of ocean freight for U.S.-flag vessels is presently limited to payment of the "ocean freight differential" which is the amount determined to represent the increased freight charges incurred by participating countries due to the requirements of the Cargo Preference Act.

In order to accomplish the purposes of Title I of the Act, it has been determined desirable to finance the ocean freight charges for shipment on foreign flag vessels to certain countries. Accordingly, this rule, in part, amends 7 CFR 17.9(g) so as to provide that the cost of ocean transportation on foreign flag vessels will be financed by CCC when, and to the extent, specifically provided in the applicable purchase authorization issued to the participating foreign country. In this manner, CCC will have flexibility in determining whether ocean freight charges on foreign flag vessels should be financed and whether to limit or condition such financing if it deems appropriate. When the purchase authorization includes the financing of ocean freight charges for foreign flag vessels, the general provisions in the regulations covering the financing of ocean freight charges would also be applicable to foreign flag vessels.

In addition to the above change, various other sections of the regulations are being amended to provide for their applicability in the event a purchase authorization provides for the financing of ocean freight charges on foreign flag vessels. In this regard particular note should be taken of the change in 7 CFR 17.8(f) which now requires the submission of reports of any payments made by suppliers of ocean transportation, either U.S.-flag or foreign flag, to representatives of the importer or importing country when ocean freight differential is paid or ocean freight financed by CCC. This regulation is based upon section 115(b) of Pub. L. 480, and would be applicable to foreign flag vessels if freight charges are financed by CCC.

This revision of the regulations is published as an interim rule to provide interested parties an opportunity to comment thereon, even though such opportunity is not required by law. Comments, in order to be considered, should be received by March 15, 1985. After review of any comments received, consideration will be given to further revisions that may be appropriate.

List of Subjects in 7 CFR Part 17

Agricultural commodities, Exports, Finance, Maritime carriers.

PART 17—[AMENDED]

Accordingly, 7 CFR Part 17, Subpart A is amended as follows: 1. The authority citation for Part 17 reads as follows:

Authority: Secs. 101–115, Pub. L. 480 83rd Cong. amended, 68 Stat. 455 (7 U.S.C. 1701 *et seq.*); E.O. 12220, 45 FR 44245.

2. In § 17.1, the last two sentences of paragraph (c)(1) are revised to read as follows:

§ 17.1 General statement.

* * * * *

(c) *Letters of commitment and reimbursement method of financing.* (1) * * * Notwithstanding any other provision of these regulations, if authorized by the purchase authorization, ocean freight or ocean freight differential shall be financed by CCC under the letter of commitment method of financing in cases where ocean freight is not included as a part of the commodity cost, subject to the applicable provisions of these regulations and such other provisions as may be specified in the purchase authorization. In such case, the supplier of ocean freight will receive payment for ocean freight or ocean freight differential as provided in these regulations and the purchase authorization under irrevocable letters of credit issued, confirmed or advised by a banking institution.

* * * * *

3. In § 17.6, paragraph (a)(5) is revised to read as follows:

§ 17.6 Contracts between suppliers and importers.

(a) *Eligibility for financing.* * * *

(5) The supplier must be engaged in the business of selling for export, or furnishing ocean transportation, from the United States and must have a person, principal or agent, on whom service of judicial process may be had in the United States. A supplier of agricultural commodities must maintain a bona-fide business office in the United States. A firm of which more than 50 percent is owned or which is controlled by a foreign government is not eligible to act as a supplier of agricultural commodities.

* * * * *

4. In § 17.8, paragraphs (f)(1) and (f)(7) are revised to read as follows:

§ 17.8 Fees, discounts, commissions, brand names, purchasing agents, shipping agents.

* * * * *

(f) *Reports required from suppliers of commodities and ocean transportation.* (1) Suppliers of (i) agricultural commodities financed under the Act and (ii) vessels on which such commodities are transported, if ocean freight or ocean freight differential is financed by CCC with respect thereto, shall report to the General Sales Manager (GSM) any commission, fee or other compensation of any kind (hereinafter referred to as "payment") which, in connection with the supplying of such commodities or vessels, is paid or to be paid by the supplier to any agent, broker, or other representative of the importer or importing country, including a corporation owned or controlled by the importer or importing counry, to which he supplies such commodities or vessels.

* * * * *

(7) If a final determination has been made under 7 CFR Part 1407 that a supplier has failed to file a report as required by this paragraph (f) or has filed a false report thereunder, the supplier shall be debarred, for a period of five years from the date of such final determination, from furnishing—directly or indirectly—commodities financed under the Act or vessels on which such commodities are to be transported if ocean freight or ocean freight differential is to be financed by CCC with respect thereto. Such supplier may also be debarred (in accordance with 7 CFR Part 1407) from participating in other programs administered or financed by CCC.

* * * * *

5. In § 17.9, paragraph (g), the first sentence of paragraph (j)(2) and the first sentence of paragraph (j)(5) are revised to read as follows:

§ 17.9 Ocean Transportation.

* * * * *

(g) *Foreign flag vessels.* The cost of ocean transportation will be financed by CCC on non-U.S. flag vessels only when, and to the extent, specifically provided in the applicable purchase authorization.

* * * * *

(j) *General financing provisions.* * * *

(2) If CCC finances ocean freight or ocean freight differential and transshipment to a foreign flag vessel occurs, CCC will finance the ocean freight or ocean freight differential, as appropriate, only to the point of transshipment, at a rate determined by the General Sales Manager, and no part of the ocean freight beyond the point of transshipment will be financed by CCC unless specifically approved by the General Sales Manager. * * *

* * * * *

(5) Freight for a vessel designated on Form CCC–106 as a U.S. flag vessel shall not be eligible for financing, unless such vessel complies with the provisions of Pub. L. 87–266. * * *

* * * * *

6. In § 17.13 the second sentence of paragraph (d)(3) introductory text is revised to read as follows. The text which follows the second sentence has not been changed and is shown for the convenience of the user.

§ 17.13 Documentation.

* * * * *

(d) *Documents required for reimbursement of ocean freight financed separately from commodity price.* * * *

(3) * * * If the invoice relates to a U.S.-flag vessel, such invoice shall contain the following typed or stamped certification, executed by the supplier:

The undersigned hereby certifies that the vessel named herein and for which ocean freight is claimed, qualifies as a privately owned U.S.-flag commercial vessel within the requirements of Pub. L. 87–266 and is an eligible U.S.-flag vessel for the purposes of Pub. L. 664, 83rd Congress.

* * * * *

Signed at Washington, D.C. on January 16, 1985.

George J. Pope,

Acting General Sales Manager, Foreign Agricultural Service.

[FR Doc. 85–1662 Filed 1–22–85; 8:45 am]

BILLING CODE 3410–10–M

Federal Crop Insurance Corporation

7 CFR Part 435

[Docket No. 1860S]

Tobacco (Quota Plan) Crop Insurance Regulations

AGENCY: Federal Crop Insurance Corporation, USDA.

ACTION: Final rule.

SUMMARY: The Federal Crop Insurance Corporation (FCIC) hereby revises and reissues the Tobacco (Quota Plan) Crop Insurance Regulations (7 CFR Part 435), effective for the 1985 and succeeding crop years to provide for: (1) Changing to a mandatory "Actual Production History" (APH) basis by removing the Premium Adjustment Table and providing for cancellation for not furnishing records; (2) adding as a cause of loss the unavoidable failure of irrigation water supply; (3) changing the method of computing indemnities when acreage, share or practice is underreported; (4) changing the definition of unit to encompass the entire ASCS farm serial number; and (5) deleting Appendix A. The intended effect of this rule is to comply with the provisions of Departmental Regulation 1512–1 with regard to review of regulations issued by FCIC for need, currency, clarity, and effectiveness. The authority for the promulgation of this rule is contained in the Federal Crop Insurance Act, as amended.

EFFECTIVE DATE: January 30, 1985.

FOR FURTHER INFORMATION CONTACT: Peter F. Cole, Secretary, Federal Crop Insurance Corporation, U.S. Department of Agriculture, Washington, D.C., 20250, telephone (202) 447–3325.

SUPPLEMENTARY INFORMATION: This action has been reviewed under USDA

procedures established by Departmental Regulation No. 1512–1 (December 15, 1983). This action constitutes a review as to the need, currency, clarity, and effectiveness of these regulations under those procedures. The sunset review date established for these regulations is August 1, 1989.

Merritt W. Sprague, Manager, FCIC, has determined that this action (1) is not a major rule as defined by Executive Order No. 12291 (February 17, 1981), because it will not result in: (a) An annual effect on the economy of $100 million or more; (b) major increases in costs or prices for consumers, individual industries, Federal, State, or local governments, or a geographical region; or (c) significant adverse effects on competition, employment, investment, productivity, innovation, or the ability of U.S.-based enterprises to compete with foreign-based enterprises in domestic or export markets; and (2) will not increase the Federal paperwork burden for individuals, small businesses, and other persons.

The title and number of the Federal Assistance Program to which this final rule apply are: Title—Crop Insurance; Number 10.450.

This program is not subject to the provisions of Executive Order 12372 which require intergovernmental consultation with State and local officials. See the Notice related to 7 CFR Part 3015, Subpart V, published at 48 FR 29115 (June 24, 1983).

This action is exempt from the provisions of the Regulatory Flexibility Act; therefore, no Regulatory Flexibility Analysis was prepared.

This action is not expected to have any significant impact on the quality of the human environment, health, and safety. Therefore, neither an Environmental Assessment nor an Environmental Impact Statement is needed.

On Tuesday, December 18, 1984, FCIC published a notice of proposed rulemaking in the **Federal Register** at 49 FR 49095, revising and reissuing the Tobacco (Quota Plan) Crop Insurance Regulations (7 CFR Part 435), effective for the 1985 and succeeding crop years. The public was given 30 days in which to submit written comments on the proposed rule.

Comments were received contending that the Actual Production History (APH) program constitutes a "mandatory Individual Yield Coverage (IYC)" program and is therefore illegal under the terms of the Crop Insurance Act, which required a pilot IYC program. FCIC rejects that contention.

The APH and IYC programs are quite different, although they share common goals. For example: IYC is an optional program; APH is not; IYC is available on a small number of crops; APH will eventually be offered on all insurable crops; Under IYC, coverage levels are adjusted at fixed rates; under APH, both coverages and rates adjusted; Under IYC, a premium adjustment table is intended to individualize rates; under APH, the premium adjustment table is not necessary because the rates are already individualized under the yield span-rating concept.

It is further clear from the statutory language, that although a pilot IYC program is required, a broad IYC program mandatory in nature is not prohibited.

Comments were also received contending that APH should be abandoned or postponed because the APH concept will lead to declining sales. The evidence does not support this contention.

In the only two crops currently being operated under the APH concept—cotton and rice—producer participation is up substantially over previous year levels. Considering the relative incompatibility of cotton and rice to the APH concept in that yield levels have been steadily declining, the increase in participation is even more telling. If anything, APH will encourge more farmers to consider crop insurance as a risk transfer program than ever before.

Since policy changes must, by contract, be on file by January 30, 1985, good cause is shown for making this rule effective immediately.

Other than minor changes in language and format, the principal changes in the tobacco policy are:

1. Section 1.a.—Add the failure of irrigation water supply because of an unavoidable cause as an insurable cause of loss. This clarifies intent since it is implied as a cause of loss in section 2.e.(2).

2. Section 5.a.—Remove the Premium Adjustment Table. The crop will be insured on an actual production history (APH) basis. Coverages will therefore reflect the actual production history of the crop on the unit. Insureds with good loss experience who are now receiving a premium discount are protected since they will retain any discount under the present schedule through the 1989 crop year or until their loss experience causes them to lose the advantage, whichever is earlier.

3. Section 5.—Remove the provisions for the transfer of insurance experience and for premium computation when participation has not been continuous. Deletion of the premium adjustment table eliminates the need for these provisions.

4. Section 15.c.—Add a clause to cancel the contract if production history is not furnished by the cancellation date. An exception will be allowed if the insured can show, prior to the cancellation date, that records are unavailable due to conditions beyond the insured's control. This clause is required by the change to mandatory APH.

5. Section 17.d.—Change the definition for the term "County" to be consistent with other marketing quota crop policies.

6. Section 17.k.—Add a definition for the term "Loss ratio" to clarify its use in section 5.

7. Section 17.s.—Change the definition of the term "Unit" to conform to a single ASCS farm serial number. No further division will be allowed. This change will reduce the problem of transferring production from one unit to another.

8. In addition to the policy changes FCIC also eliminates the codification of Appendix A. All FCIC service offices in the United States will be able to advise a producer if tobacco insurance is offered in any county.

List of Subjects in 7 CFR Part 435

Crop insurance, Tobacco (Quota Plan)

Final Rule

Accordingly, pursuant to the authority contained in the Federal Crop Insurance Act, as amended (7 U.S.C. 1501 *et seq.*), the Federal Crop Insurance Corporation hereby revises and reissues the Tobacco (Quota Plan) Crop Insurance Regulations (7 CFR Part 435), effective for the 1985 and succeeding crop years, to read as follows:

PART 435—TOBACCO (QUOTA PLAN) CROP INSURANCE REGULATIONS

Subpart—Regulations for the 1985 and Succeeding Crop Years

Sec.

435.1 Availability of quota plan tobacco crop insurance.
435.2 Premium rates, production guarantees, coverage levels, and prices at which indemnities shall be computed.
435.3 OMB control numbers.
435.4 Creditors.
435.5 Good faith reliance on misrepresentation.
435.6 The contract.
435.7 The application and policy.

Authority: Secs. 506, 516, Pub. L. 75–430, 52 Stat. 73, 77 as amended (7 U.S.C. 1506, 1516).

Subpart—Regulations for the 1985 and Succeeding Crop Years

§ 435.1 Availability of quota plan tobacco crop insurance.

Insurance shall be offered under the provisions of this subpart on tobacco in counties within the limits prescribed by and in accordance with the provisions of the Federal Crop Insurance Act, as amended. The counties shall be designated by the Manager of the Corporation from those approved by the Board of Directors of the Corporation.

§ 435.2 Premium rates, production guarantees, coverage levels, and prices at which indemnities shall be computed.

(a) The Manager shall establish premium rates, production guarantees, coverage levels, and prices at which indemnities shall be computed for tobacco which will be included in the actuarial table on file in service offices for the county and which may be changed from year to year.

(b) At the time application for insurance is made, the applicant will elect a coverage level and price at which indemnities will be computed from among those levels and prices contained in the actuarial table for the crop year.

§ 435.3 OMB control numbers.

The information collection requirements contained in these regulations (7 CFR Part 435) have been approved by the Office of Management and Budget (OMB) under the provisions of 44 U.S.C. Chapter 35 and have been assigned OMB Nos. 0563–0003 and 0563–0007.

§ 435.4 Creditors.

An interest of a person in an insured crop existing by virtue of a lien, mortgage, garnishment, levy, execution, bankruptcy, involuntary transfer or other similar interest shall not entitle the holder of the interest to any benefit under the contract.

§ 435.5 Good faith reliance on misrepresentation.

Notwithstanding any other provision of the tobacco insurance contract, whenever—

(a) An insured person under a contract of crop insurance entered into under these regulations, as a result of a misrepresentation or other erroneous action or advice by an agent or employee of the Corporation (1) is indebted to the Corporation for additional premiums, or (2) has suffered a loss to a crop which is not insured or for which the insured person is not entitled to an indemnity because of failure to comply with the terms of the insurance contract, but which the insured person believed to be insured, or believed the term of the insurance contract to have been complied with or waived, and

(b) The Board of Directors of the Corporation, or the Manager in cases involving not more than $100,000.00, finds that: (1) An agent or employee of the Corporation did in fact make such misrepresentation or take other erroneous action or give, erroneous advice; (2) said insured person relied thereon in good faith; and (3) to required the payment of the additional premiums or to deny such insured's entitlement to the indemnity would not be fair and equitable, such insured person shall be granted relief the same as if otherwise entitled thereto.

Application for relief under this section must be submitted to the Corporation in writing.

§ 435.6 The contract.

The insurance contract shall become effective upon the acceptance by the Corporation of a duly executed application for insurance on a form prescribed by the Corporation. The contract shall cover the tobacco crop as provided in the policy. The contract shall consist of the application, the policy, and the county actuarial table. Any changes made in the contract shall not affect its continuity from year to year. The forms referred to in the contract are available at the applicable service offices.

§ 435.7 The application and policy.

(a) Application for insurance on a form prescribed by the Corporation may be made by any person to cover such person's share in the tobacco crop as landlord, owner-operator, or tenant. The application shall be submitted to the Corporation at the service office on or before the applicable closing date on file in the service office.

(b) The Corporation may discontinue the acceptance of applications in any county upon its determination that the insurance risk is excessive, and also, for the same reason, may reject any individual application. The Manager of the Corporation is authorized in any crop year to extend the closing date for submitting applications in any county, by placing the extended date on file in the applicable service offices and publishing a notice in the **Federal Register** upon the Manager's determination that no adverse selectivity will result during the period of such extension. However, if adverse conditions should develop during such period, the Corporation will immediately discontinue the acceptance of applications.

(c) In accordance with the provisions governing changes in the contract contained in policies issued under FCIC regulations for the 1985 and succeeding crop years, a contract in the form provided for in this subpart will come into effect as a continuation of a tobacco contract issued under such prior regulations, without the filing of a new application.

(d) The application for the 1985 and succeeding crop years is found at Subpart D of Part 400—General Administrative Regulations (7 CFR 400.37, 400.38) and may be amended from time to time for subsequent crop years. The provisions of the Tobacco (Quota Plan) Insurance Policy for the 1985 and succeeding crop years are as follows:

DEPARTMENT OF AGRICULTURE

Federal Crop Insurance Corporation

Quota Plan of Tobacco—Crop Insurance Policy

(This is a continuous contract. Refer to Section 15.)

AGREEMENT TO INSURE: We will provide the insurance described in this policy in return for the premium and your compliance with all applicable provisions.

Throughout this policy, "you" and "your" refer to the insured shown on the accepted Application and "we, "us" and "our" refer to the Federal Crop Insurance Corporation.

Terms and Conditions

1. Causes of loss.

a. The insurance provided is against unavoidable loss of production resulting from the following causes occurring within the insurance period:

(1) Adverse weather conditions;
(2) Fire;
(3) Insects;
(4) Plant disease;
(5) Wildlife;
(6) Earthquake;
(7) Volcanic eruption; or
(8) Failure of the irrigation water supply due to an unavoidable cause occurring after the beginning of planting;

unless those causes are excepted, excluded, or limited by the actuarial table or section 9d(8).

b. We will not insure against any loss of production due to:

(1) The neglect, mismanagement or wrongdoing of you, any member of your household, your tenants or employees;

(2) The failure to follow recognized good tobacco farming practices;

(3) The impoundment of water by any governmental, public or private dam or reservoir project; or

(4) Any cause not specified in section 1a as an insured loss.

2. Crop, acreage, insured poundage quota, and share insured.

a. The crop insured will be tobacco of the type shown as insurable in the actuarial table, which is grown on insured acreage, and

for which a premium rate is provided by the actuarial table.

b. The acreage insured for each crop year will be an insurable type of tobacco planted on insurable acreage and in which you have a share, as reported by you or as determined by us, whichever we elect.

c. The insured share will be your share as landlord, owner-operator, or tenant in the insured tobacco at the time of planting.

d. We do not insure any acreage:

(1) If the farming practices carried out are not in accordance with the farming practices for which the premium rates have been established;

(2) On which the tobacco was destroyed for the purpose of conforming with any other program administered by the United States Department of Agriculture;

(3) Which is destroyed, it is practical to replant to tobacco, and such acreage was not replanted;

(4) Initially planted after the final planting date contained in the actuarial table, unless you agree to coverage reduction on our form;

(5) Planted to tobacco of a discount variety under provisions of the tobacco price support program;

(6) Planted to a type or variety of tobacco not established as adapted to the area or excluded by the actuarial table;

(7) Designated as uninsurable by the actuarial table; or

(8) Planted for experimental purposes.

e. The insured poundage quota for each crop year will be the effective poundage marketing quota applicable to the unit as provided under ASCS Tobacco Marketing Quota Regulations for the crop year plus any additional poundage you intend to produce on the unit that crop year, as reported by you or as determined by us, whichever we elect.

However:

(1) The insured poundage quota may not include any amount which would be subject to a marketing quota penalty under ASCS Tobacco Marketing Quota Regulations;

(2) The poundage marketing quota may be reduced for any carryover tobacco to be marketed under the poundage quota applicable to the unit when such poundage reduction is clearly specified by you in filing the acreage and quota report;

(3) The insured poundage quota will never exceed the pounds obtained by multiplying the insured acres by the applicable farm yield per acre; and

(4) Unless otherwise provided by the actuarial table, for any crop year in which tobacco poundage marketing quota regulations are not in effect, the insured poundage quota will be the pounds obtained by multiplying the applicable farm yield per acre times the lower of the reported or insured acreage on the unit.

f. If insurance is provided for an irrigated practice:

(1) You must report as irrigated only the acreage for which you have adequate facilities and water to carry out a good tobacco irrigation practice at the time of planting; and

(2) Any loss of production caused by failure to carry out a good tobacco irrigation practice, except failure of the water supply from an unavoidable cause occurring after the beginning of planting, will be considered as due to an uninsured cause. The failure or breakdown of irrigation equipment or facilities will not be considered as a failure of the water supply from an unavoidable cause.

(3) Insurance will not attach on an irrigated basis to acreage otherwise insurable on such basis unless it is designated as irrigated at the time the acreage is reported.

g. We may limit the insured acreage to any acreage limitation established under any Act of Congress, if we advise you of the limit prior to planting.

3. Report of acreage, share, and poundage quota.

You must report on our form:

a. All the acreage of insurable types of tobacco in the county in which you have a share;

b. Your share at the time of planting; and

c. The effective poundage marketing quota applicable to the unit as provided under ASCS Tobacco Marketing Quota Regulations plus any additional poundage you intend to produce on the unit in that crop year. Such poundage marketing quota may be reduced for any carryover tobacco to be marketed under the poundage quota applicable to the unit provided such poundage reduction is clearly specified in filing the acreage and quota report. The quota so reported will not be subject to change by you.

You must designate separately any acreage that is not insurable. You must report if you do not have a share in any tobacco planted in the county. This report must be submitted annually on or before the reporting date established by the actuarial table. All indemnities may be determined on the basis of information you have submitted on this report. If you do not submit this report by the reporting date, we may elect to determine by unit the insured acreage, share, and practice or we may deny liability on any unit. Any report submitted by you may be revised only upon our approval.

4. Amounts of insurance and coverage levels.

a. The coverage levels are contained in the actuarial table.

b. The amount of insurance for a unit will be the dollar amount determined by multiplying the insured poundage quota for the unit by the percentage guarantee for the applicable coverage level established by the actuarial table and multiplying this product by the current year's support price for type 31 tobacco (rounded to the nearest cent) less six cents per pound for warehouse charges.

c. Coverage level 2 will apply if you have not elected a coverage level.

d. You may change the coverage level on or before the closing date for submitting applications for the crop year as established by the actuarial table.

5. Annual premium.

a. The annual premium is earned and payable at the time of planting. The amount is computed by multiplying the amount of insurance for the unit times the premium rate, times your share at the time of planting.

b. Interest will accrue at the rate of one and one-half percent (1½%) simple interest per calendar month, or any part thereof, on any unpaid premium balance starting on the first day of the month following the first premium billing date.

c. If you are eligible for a premium reduction in excess of 5 percent based on your insuring experience through the 1983 crop year under the terms of the Experience Table contained in the tobacco policy for the 1984 crop year, you will continue to receive the benefit of that reduction subject to the following conditions:

(1) No premium reduction will be retained after the 1989 crop year;

(2) The premium reduction will not increase because of favorable experience;

(3) The premium reduction will decrease because of unfavorable experience in accordance with the terms of the 1984 policy;

(4) Once the loss ratio exceeds .80 no further premium reduction will apply; and

(5) Participation must be continuous.

6. Deductions for debt.

Any unpaid amount due us may be deducted from any indemnity payable to you or from any loan or payment due you under any Act of Congress or program administered by the United States Department of Agriculture or its Agencies.

7. Insurance period.

Insurance attaches when the tobacco is planted and ends at the earliest of:

a. Total destruction of the tobacco;

b. Weighing-in at the tobacco warehouse;

c. Removal of the tobacco from the unit (except for curing, grading, packing or immediate delivery to the tobacco warehouse);

d. Final adjustment of a loss; or

e. February 28, immediately following the normal harvest period.

8. Notice of damage or loss.

a. In case of damage or probable loss:

(1) You must give us written notice if:

(a) During the period before harvest, the tobacco on any unit is damaged and you decide not to further care for or harvest any part of it;

(b) You want our consent to put the acreage to another use; or

(c) After consent to put acreage to another use is given, additional damage occurs.

Insured acreage may not be put to another use until we have appraised the tobacco and given written consent. We will not consent to another use until it is too late to replant. You must notify us when such acreage is put to another use.

(2) You must give us notice at least 15 days before the beginning of harvest if you anticipate a loss on any unit.

(3) If probable loss is later determined, immediate notice must be given. A representative sample of the unharvested tobacco (at least 10 feet wide and the entire length of the field) must remain unharvested for a period of 15 days from the date of notice, unless we give you written consent to harvest the sample.

(4) Notice must be given immediately if any tobacco is destroyed or damaged by fire during the insurance period.

(5) If tobacco is not to be sold through auction warehouses and an indemnity is to be claimed, notice must be given in sufficient time to allow us to inspect the cured tobacco prior to its sale or other disposition.

(6) In addition to the notices required by this section, if you are going to claim an indemnity on any unit, we must be given notice not later than 30 days after the earliest of:

(a) Total destruction of the tobacco on the unit;

(b) The date marketing or other disposal of the insured tobacco on the unit is completed; or

(c) The calendar date for the end of the insurance period.

b. You must obtain written consent from us before you destroy any of the tobacco which is not to be harvested.

c. We may reject any claim for indemnity if any of the requirements of this section or section 9 are not complied with.

9. Claim for indemnity.

a. Any claim for indemnity on a unit must be submitted to us on our form not later than 60 days after the earliest of:

(1) Total destruction of the tobacco on the unit;

(2) The date marketing or other disposal of the insured tobacco on the unit is completed; or

(3) The calendar date for the end of the insurance period.

b. We will not pay any indemnity unless you:

(1) Establish the total production of tobacco on the unit and that any loss of production has been directly caused by one or more of the insured causes during the insurance period; and

(2) Furnish all information we require concerning the loss.

c. The indemnity will be determined on each unit by:

(1) Subtracting from the amount of insurance for the unit, the value of the total production of tobacco to be counted (see section 9d); and

(2) Multiplying the remainder by your share.

d. The value of the total production to be counted for a unit will include the value of all harvested and appraised production.

(1) Production to count will include:

(a) The gross returns (less six cents per pound for warehouse charges) from tobacco sold on the warehouse floor;

(b) The fair market value of the tobacco sold other than on the warehouse floor;

(c) The fair market value of the tobacco harvested and not sold;

(d) The fair market value of any unharvested tobacco as if such tobacco were harvested and cured; and

(e) The current year's support price per pound (less six cents per pound for warehouse charges) for appraisals made by us for poor farming practices or uninsured causes of loss. (If a price support program is not in effect, such appraised production will be valued at the market price for the current crop year.)

(2) To enable us to determine the fair market value of tobacco not sold through auction warehouses, we must be given the opportunity to inspect such tobacco before it is sold, contracted to be sold, or otherwise disposed of and, if the best offer you receive for any such tobacco is considered by us to be inadequate, to obtain additional offers on your behalf.

(3) The value of appraised production to be counted will include:

(a) The value of unharvested production on harvested acreage and potential production lost due to uninsured causes and failure to follow recognized good tobacco farming practices;

(b) Not less than the average amount of insurance per insured acre for the unit for any acreage which is abandoned or put to another use without our prior written consent or damaged solely by an uninsured cause;

(c) Not less than 35 percent of the average amount of insurance per insured acre for the unit for all other unharvested acreage.

(4) Any appraisal we have made on insured acreage for which we have given written consent to be put to another use will be considered production unless such acreage is:

(a) Not put to another use before harvest of tobacco becomes general in the county;

(b) Harvested; or

(c) Further damaged by an insured cause before the acreage is put to another use.

(5) The amount of production of any unharvested tobacco may be determined on the basis of field appraisals conducted after the end of the normal harvest period.

(6) If you have elected to exclude hail and fire as insured causes of loss and the tobacco is damaged by hail or fire, appraisals will be made in accordance with Form FCI–78, "Request to Exclude Hail and Fire".

(7) The commingled production of units will be allocated to such units in proportion to our liability on the harvested acreage of each unit.

e. You must not abandon any acreage to us.

f. You may not bring suit or action against us unless you have complied with all policy provisions. If a claim is denied, you may sue us in the United States District Court under the provisions of 7 U.S.C. 1506(c). You must bring suit within 12 months of the date notice of denial is mailed to and received by you.

g. We will pay the loss within 30 days after we reach agreement with you or entry of a final judgment. In no instance will we be liable for interest or damages in connection with any claim for indemnity, whether we approve or disapprove such claim.

h. If you die, disappear, or are judicially declared incompetent, or if you are an entity other than an individual and such entity is dissolved after the tobacco is planted for any crop year, any indemnity will be paid to the person(s) we determine to be benefically entitled thereto.

i. If you have other fire insurance, fire damage occurs during the insurance period, and you have not elected to exclude fire insurance from this policy, we will be liable for loss due to fire only for the smaller of:

(1) The amount of indemnity determined pursuant to this contract without regard to any other insurance; or

(2) The amount by which the loss from fire exceeds the indemnity paid or payable under such other insurance. For the purposes of this section, the amount of loss from fire will be the difference between the fair market value of the production on the unit before the fire and after the fire.

10. Concealment or fraud.

We may void the contract on all crops insured without affecting your liability for premiums or waiving any right, including the right to collect any amount due us if, at any time, you have concealed or misrepresented any material fact or committed any fraud relating to the contract, and such voidance will be effective as of the beginning of the crop year with respect to which such act or omission occurred.

11. Transfer of right to indemnity on insured share.

If you transfer any part of your share during the crop year, you may transfer your right to an indemnity. The transfer must be on our form and approved by us. We may collect the premium from either you or your transferee or both. The transferee will have all rights and responsibilities under the contract.

12. Assignment of indemnity.

You may assign to another party your right to an indemnity for the crop year, only on our form and with our approval. The assignee will have the right to submit the loss notices and forms required by the contract.

13. Subrogation. (Recovery of loss from a third party.)

Because you may be able to recover all or a part of your loss from someone other than us, you must do all you can to preserve any such rights. If we pay you for your loss then your right of recovery will at our option belong to us. If we recover more than we paid you plus our expenses, the excess will be paid to you.

14. Records and access to farm.

You must keep, for two years after the time of loss, records of the harvesting, storage, shipment, sale or other disposition of all tobacco produced on each unit including separate records showing the same information for production from any uninsured acreage. Any person designated by us will have access to such records and the farm for purposes related to the contract.

15. Life of contract: Cancellation and termination.

a. This contract will be in effect for the crop year specified on the application and may not be canceled by you for such crop year. Thereafter, the contract will continue in force for each succeeding crop year unless canceled or terminated as provided in this section.

b. This contract may be canceled by either you or us for any succeeding crop year by giving written notice on or before the cancellation date preceding such crop year.

c. This contract will be canceled if you do not furnish satisfactory records of the previous year's production to us on or before the cancellation date. If the insured, prior to the cancellation date, shows, to our satisfaction, that records are unavailable due to conditions beyond the insured's control such as fire, flood or other natural disaster, the Field Actuarial Office may assign a yield for that year. The assigned yield will not exceed the ten-year average.

d. This contract will terminate as to any crop year if any amount due us on this or any other contract with you is not paid on or before the termination date preceding such crop year for the contract on which the amount is due. The date of payment of the amount due:

(1) If deducted from an indemnity will be the date you sign the claim; or

(2) If deducted from payment under another program administered by the United States Department of Agriculture will be the date both such other payment and set off are approved.

e. The cancellation and termination dates are April 15.

f. If you die or are judicially declared incompetent, or if you are an entity other than an individual and such entity is dissolved, the contract will terminate as of the date of death, judicial declaration, or dissolution. If such event occurs after insurance attaches for any crop year, the contract will continue in force through the crop year and terminate at the end thereof. Death of a partner in a partnership will dissolve the partnership unless the partnership agreement provides otherwise. If two or more persons having a joint interest are insured jointly, death of one of the persons will dissolve the joint entity.

g. The contract will terminate if no premium is earned for five consecutive years.

16. Contract changes.

We may change any of the terms and provisions of the contract from year to year. All contract changes will be available at your service office by December 31 preceding the cancellation date (January 30 for the 1985 crop year only). Acceptance of any changes will be conclusively presumed in the absence of any notice from you to cancel the contract.

17. Meaning of terms.

For the purposes of quota tobacco crop insurance:

a. "Actuarial table" means the forms and related material for the crop year approved by us which are available for public inspection in your service office, and which show the coverage levels, premium rates, practices, insurable and uninsurable acreage, and related information regarding tobacco insurance in the county.

b. "ASCS" means the Agricultural Stabilization and Conservation Service of the United States Department of Agriculture.

c. "Carryover tobacco" means any tobacco on hand from the previous year's production.

d. "County" means the county shown on the application and:

(1) Any additional land located in a local producing area bordering on the county, as shown by the actuarial table; and

(2) Any land identified by an ASCS Farm Serial Number for the county but physically located in another county.

e. "Crop year" means the period within which the tobacco is normally grown and will be designated by the calendar year in which the tobacco is normally harvested.

f. "Effective poundage marketing quota" means the farm marketing quota as established and recorded by ASCS.

g. "Farm yield" means the yield per acre used by ASCS in establishing the basic farm marketing poundage quota for the tobacco farm, unless we have established a yield for the farm in the actuarial table.

h. "Harvest" means the completion of cutting of tobacco on any acreage from which acreage at least 20 percent of the amount of tobacco in pounds per acre (obtained by multiplying the applicable insured poundage quota for the unit by the applicable percentage of guarantee shown in the actuarial table for such acreage and dividing this result by the insured acreage in the unit) is cut.

i. "Insurable acreage" means that acreage planted to an insurable type of tobacco excluding any acreage designated as noninsurable by the actuarial table.

j. "Insured" means the person who submitted the application accepted by us.

k. "Loss ratio" means the ratio of indemnity(ies) to premium(s).

l. "Market Price" for a crop year means the average auction price for the applicable type (less six cents per pound for warehouse charges) in the belt or area. The market price will be designated by the actuarial table.

m. "Person" means an individual, partnership, association, corporation, estate, trust, or other business enterprise or legal entity, and wherever applicable, a State, a political subdivision of a State, or any agency thereof.

n. "Planting" means transplanting the tobacco plant from the bed to the field.

o. "Rounded" means rounding up for ½ and above and rounding down for less than ½.

p. "Service office" means the office servicing your contract as shown on the application for insurance or such other approved office as may be selected by you or designated by us.

q. "Support price per pound" means the average price support level per pound for the insured type of tobacco as announced by the United States Department of Agriculture under the tobacco price support program. For any crop year in which a price support for the insured type is not in effect, the market price for that crop year will be used.

r. "Tenant" means a person who rents land from another person for a share of the tobacco or a share of the proceeds therefrom.

s. "Unit" means all insurable acreage of an insurable type of tobacco in the county in which you have an insured share on the date of planting for the crop year and which is identified by a single ASCS Farm Serial Number at the time insurance first attaches under this policy for the crop year. Units will be determined when the acreage is reported. We may reject or modify any ASCS reconstitution for the purpose of unit definition if the reconstitution was in whole or part to defeat the purpose of the Federal Crop Insurance Program or to gain disproportionate advantage under this policy. Errors in reporting units may be corrected by us when adjusting a loss.

18. Descriptive headings.

The descriptive headings of the various policy terms and conditions are formulated for convenience only and are not intended to affect the construction or meaning of any of the provisions of the contract.

19. Determinations.

All determinations required by the policy will be made by us. If you disagree with our determinations, you may obtain reconsideration of or appeal those determinations in accordance with Appeal Regulations.

20. Notices.

All notices required to be given by you must be in writing and received by your service office within the designated time unless otherwise provided by the notice requirement. Notices required to be given immediately may be by telephone or in person and confirmed in writing. Time of the notice will be determined by the time of our receipt of the written notice.

Done in Washington, D.C., on January 18, 1985.

Peter F. Cole,

Secretary, Federal Crop Insurance Corporation.

Dated: January 15, 1985.

Merritt W. Sprague,

Manager.

[FR Doc. 85-1668 Filed 1-22-85; 8:45 am]

BILLING CODE 3410-08-M

Agricultural Marketing Service

7 CFR Part 982

Filberts/Hazelnuts Grown in Oregon and Washington; Establishment of Inshell Trade Demand and Final Free and Restricted Percentages for the 1984-85 Marketing Year

Correction

In FR Doc. 85-1412, beginning on page 2539, in the issue of Thursday, January 17, 1985, on page 2541, in the first column, in the table, in the first line, "July 1, 1985" should read "July 1, 1984".

BILLING CODE 1505-01-M

Animal and Plant Health Inspection Service

9 CFR Part 97

[Docket No. 84-123]

Overtime Services Relating to Imports and Exports; Commuted Traveltime Allowances

AGENCY: Animal and Plant Health Inspection Service, USDA.

ACTION: Final rule.

SUMMARY: This document amends the administrative instructions prescribing commuted traveltime allowances by adding an allowance of one hour for the metropolitan area of Bozeman, Montana. This amendment is intended to reflect the time spent in reporting to and returning from the place at which an

employee of Veterinary Services performs overtime or holiday duty. This amendment is necessary in order to advise the public of the addition of a service area and the traveltime allowance for that area.

EFFECTIVE DATE: January 23, 1985.

FOR FURTHER INFORMATION CONTACT: Louise Rakestraw Lothery, Assistant Executive Officer, VS, APHIS, USDA, Room 857, Federal Building, 6505 Belcrest Road, Hyattsville, MD 20782, 301–436–8511.

SUPPLEMENTARY INFORMATION:

Background

The regulations in 9 CFR Part 97, "Overtime Services Relating to Imports and Exports," (referred to below as the regulations) set forth provisions for obtaining, on a reimburseable basis, inspection, quarantine, and other services pertaining to the importation and exportation of animals during Sundays, holidays or at times outside the regular tour of duty of the employees of Veterinary Services (VS) who perform such services. The inspection, quarantine, and other reimbursable overtime services authorized by 7 U.S.C. 2260 are provided upon request by any person, firm, or corporation having ownership, custody, or control of the animals or articles requiring such services.

Section 97.2 of the regulations contains administrative instructions prescribing commuted traveltime periods. Traveltime allowances reflect, as nearly as is practicable, the time, measured in hours, required for a VS employee to travel from the office where the employee is stationed to the locality where the reimbursable overtime service is provided.

This document amends § 97.2 of the regulations by adding Bozeman, Montana, as a location serviced by VS employees and by adding a commuted traveltime allowance of one hour for the metropolitan area of Bozeman. The amendment is intended to reflect the time spent in reporting to and returning from the place at which an employee of Veterinary Service performs overtime or holiday duty. A traveltime allowance may be included in determining the charge assessed the recipient of the reimbursable overtime service provided.

Executive Order, Regulatory Flexibility Act, and Effective Date

This rule is issued in conformance with Executive Order 12291 and has been determined to be not a major rule. Based on information compiled by the Department, it has been determined that this rule will not have a significant effect on the econony; will not cause a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; and will not cause adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets. Also, the Administrator of the Animal and Plant Health Inspection Service has determined that this action will not have a significant economic impact on a substantial number of small entities.

Specifically, this amendment affects only those entities that request the services of an inspector in the Bozeman, Montana, metropolitan area on a Sunday, a holiday, or on an overtime basis. Services of an inspector during regularly established hours of service at a port are still furnished free of charge to those requiring the services. The pay provisions appropriate for employees performing inspection and quarantine services at ports of entry, and the features of the reimbursable plan for recovering the costs of furnishing port of entry inspection depend upon facts within the knowledge of the Department of Agriculture. It does not appear that public participation in this rulemaking proceeding would make additional relevant information available to the Department.

Accordingly, pursuant to the administrative procedure provisions in 5 U.S.C. 533, it is found upon good cause that prior notice and other public procedures with respect to this rule are impracticable, unnecessary, and contrary to the public interest, and good cause is found for making this rule effective less than 30 days after publication of this document in the **Federal Register**.

List of Subjects in 9 CFR Part 97

Exports, Government employees, Imports, Livestock and livestock products, Poultry and poultry products, Transportation.

PART 97—OVERTIME SERVICES RELATING TO IMPORTS AND EXPORTS

Therefore, § 97.2 of 9 CFR is amended by revising the entries in the table for Montana, as follows:

§ 97.2 Administrative instructions prescribing commuted traveltime.

* * * * *

COMMUTED TRAVEL ALLOWANCES

[In hours]

Location covered	Served from	Metropolitan area	
		Within	Outside
* * * * *			
Montana:			
Bozeman		1	
Great Falls Airport.	Vaughn	1	
Port of Opheim	Opheim		1
Do.	Wolf Point		5
Port of Raymond.	Raymond		1
Port of Sweetgrass.	Great Falls		5
Sweetgrass		1	
* * * * *			

Authority: 64 Stat. 561; 7 U.S.C. 2260; 7 CFR 2.17, 2.51, 371.2(d).

Done at Washington, D.C. this 16th day of January, 1985.

K.R. Hook,

Acting Deputy Administrator, Veterinary Services.

[FR Doc. 85–1661 Filed 1–22–85; 8:45 am]

BILLING CODE 3410-34-M

SECURITIES AND EXCHANGE COMMISSION

17 CFR Parts 240, 249, 270, and 274

[Release No. 34–21633A; IC–14299A; S7–1–85]

Semi-Annual Report Form for Registered Investment Companies; Temporary Suspension of Quarterly Reporting Obligations of Certain Registered Investment Companies Pending Receipt of Comments on Proposed Final Action; Correction

AGENCY: Securities and Exchange Commission.

ACTION: Adoption of form, rules and rule revisions; withdrawal of forms and rescission of rules; temporary adoption of rules and certain form items with solicitation of comment on final action; correction.

SUMMARY: This document corrects a final rule which was published January 11, 1985 (50 FR 1442) relating to forms that registered investment companies will be required to file with the Commission. The correction concerns notification of inability to timely file all or any required portion of a Form 10–K, 20–F, 11–K, N–SAR or 10–Q.

FOR FURTHER INFORMATION CONTACT: Elizabeth K. Norsworthy, Chief, Office or Regulatory Policy, (202) 272–2048 or John Banks-Brooks, Esq., Office of Disclosure Policy and Investment Adviser Regulation, (202) 272–7313, Division of Investment Management, Securities and Exchange Commission.

SUPPLEMENTARY INFORMATION: The following correction is made at FR Doc. 85–842 appearing on page 1442 in the issue of January 11, 1985.

§ 240.12b–25 [Corrected]

1. Paragraph (b)(2)(ii) is corrected to read as follows:

* * * * *

(b) * * *

(2) * * *

(ii) Either the subject annual report or semi-annual report/portion thereof will be filed no later than the fifteenth calendar day following the prescribed due date or the subject quarterly report/portion thereof will be filed no later than the fifth calendar day following the prescribed due date; and

* * * * *

John Wheeler,

Secretary.

January 15, 1985.

[FR Doc. 85–1634 Filed 1–22–85; 8:45 am]

BILLING CODE 8010–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 182

[Docket No. 84A–0370]

Notice to Shippers, Distributors, Packers, and Importers of Shrimp Containing Sulfites

AGENCY: Food and Drug Administration.

ACTION: Rule-related notice.

SUMMARY: The Food and Drug Administration (FDA) is advising domestic shippers, distributors, packers, and importers of shrimp and all other interested persons that it is not consistent with current good manufacturing practice to use sulfites in shrimp in amounts that exceed that necessary for the prevention of black spotting (melanosis). FDA has determined that use of sulfites in accordance with current good manufacturing practice will result in a sulfite residue in the shrimp of from 60 to 100 parts per million (ppm). FDA is also advising the shrimp industry that foods containing preservatives must bear labeling stating that fact. Therefore, shrimp products in packaged form that have been treated with sulfiting agents must bear labeling declaring their presence as preservatives. The lack of such labeling constitutes misbranding. The reason for issuance of this notice is to inform the shrimp industry of FDA's concern about the presence of undeclared sulfiting agents in shrimp and of its concern about the use of sulfiting agents at levels in excess of those necessary to achieve their intended effect.

FOR FURTHER INFORMATION CONTACT: John M. Taylor, Center for Food Safety and Applied Nutrition (HFF–310), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–485–0187.

SUPPLEMENTARY INFORMATION:

I. Introduction

Sulfiting agents are added to a variety of foods as preservatives. They are used in the processing of shrimp to prevent melanosis or black spotting. Melanosis is the enzymatic reaction of naturally occurring chemicals in the shrimp shell that results in black discoloration of the shrimp. The addition of a sulfiting agent (a preservative) prevents this reaction from taking place, and the shrimp do not darken. Under section 403(k) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 343(k)), foods that contain preservatives must bear labeling stating that fact.

II. Regulatory History

The six sulfiting agents are listed in Part 182 of FDA's regulations (21 CFR Part 182) as ingredients whose use as chemical preservatives is generally recognized as safe (GRAS). The inclusion of potassium bisulfite (21 CFR 182.3616), potassium metabisulfite (21 CFR 182.3637), sodium bisulfite (21 CFR 182.3739), sodium metabisulfite (21 CFR 182,3766), sodium sulfite (21 CFR 182.3798), and sulfur dioxide (21 CFR 182.3862) on the GRAS list was effectuated by a final rule published in the **Federal Register** of November 20, 1959 (24 FR 9368), and subsequent recodification.

The fact that a substance is listed in Part 182 does not mean, however, that it can be safely used at any level in food. The regulation for each of these substances states that the substance is GRAS when used in accordance with good manufacturing practice. Section 182.1(b) defines good manufacturing practice to impose certain restrictions on the use of the substance. Among these restrictions is the requirement that: "The quantity of a substance added to food does not exceed the amount reasonably required to accomplish its intended physical, nutritional, or other technical effect in food, * * *." FDA now uses the phrase "current good manufacturing practice" (CGMP) in place of "good manufacturing practice." Consequently, the agency will use the abbreviation "CMGP" throughout the remainder of this document.

Under § 182.1(b), the CGMP level of use will vary from ingredient to ingredient and depend upon the intended technical effect. Normally the CGMP level is determined by the acceptable practices of the industry. FDA's policy is that it is the responsibility of the individual manufacturer to determine what level of a particular ingredient is suffient to achieve the intended technical effect and thus is CGMP.

III. The GRAS Review

In 1970, FDA announced that it was undertaking a comprehensive review of the substances on the GRAS list (35 FR 18623; December 8, 1970). The purpose of this review is to evaluate under current standards the available safety information on each substance on the GRAS list and, on the basis of that evaluation, to affirm the substance as GRAS, to approve its use as a food additive, or to interim list the substance pending completion of additional toxicity experiments. *Id.* The substances whose use the agency has affirmed as GRAS are listed in Part 184 (21 CFR Part 184) if they are direct food ingredients, or in Part 186 (21 CFR Part 186) if they are indirect food ingredients.

In the GRAS review, FDA initially included a description of the CGMP conditions of use (technical effects and food categories, as well as levels of use) in the GRAS affirmation regulation for each substance. However, during the review, in response to numerous industry comments, FDA determined that it was not necessary to include such a description in the regulations for most substances (48 FR 48457, 48458; October 19, 1983). The agency consequently stated that it would only specify those CGMP conditions of use that are necessary to ensure continued safe use of the ingredient. *Id.*

In 1982, FDA proposed to affirm that potassium metabisulfite, sodium bisulfite, sodium metabisulfite, and sulfur dioxide are GRAS, with specific limitations on their use, as direct human food ingredients (47 FR 29956; July 9, 1982). In response to that proposal, the agency received a large number of comments that contained much new information on the use of sulfites. A number of comments concerned experiences involving allergic-type reactions apparently caused by foods containing sulfiting agents. Subsequently, FDA referred all available information to the Federation of American Societies for Experimental Biology (FASEB) for further review.

In the **Federal Register** of July 9, 1984 (49 FR 27995), FDA announced that the

Life Sciences Research Office of FASEB had formed an ad hoc Review Panel to study the available information on the health effects of sulfiting agents. The ad hoc Review Panel made its tentative report public on October 15, 1984 (49 FR 42984; October 25, 1984). One of the recommendations contained in the tentative report is that studies should be undertaken to investigate the relationship between sulfiting agents and the hypersensitivity reactions that have been reported.

IV. Adulteration and Misbranding of Shrimp Products

Because of the public health issues raised by some of the data submitted in response to the 1982 GRAS affirmation proposal, FDA has been concerned that, while it completes its review of those data, sulfites be used at levels that comply with CGMP. In addition, the agency has tried to ensure that food products containing sulfites are properly labeled.

As a result, FDA has investigated the levels at which sulfiting agents are being added to food and the labeling of products that contain sulfites as a preservative. Based on complaints that the agency has received and on its own investigation, FDA has become aware that there is particular confusion in the shrimp industry about the CGMP residual level for sulfites in this food. Moreover, the agency has discovered that the presence of sulfites is not being declared on the label of shrimp products in package form.

During the course of FDA's investigation, it has learned that even when the sulfiting agents are used in accordance with CGMP, there is considerable variation in the residue level on the shrimp, calculated as sulfur dioxide. The agency now has new data that indicate that the presence of sulfite residue on shrimp that have been processed in accordance with CGMP is in the range of 60 to 100 ppm. The agency therefore considers that the presence of sulfite residues of more than 100 ppm is an indication of use of sulfiting agents in processing the shrimp at levels that are not GRAS. Shrimp products that contain excess amounts of sulfiting agents are thus adulterated because they contain an unsafe food additive under sections 409 and 402(a)(2)(C) of the act (21 U.S.C. 348 and 342(a)(2)(C)).

To eliminate the confusion that exists in the shrimp industry and to ensure the continued safe use of sulfites in shrimp, FDA is taking this opportunity to advise all interested persons of the level of sulfites in shrimp that is CGMP under 21 CFR 182.1(b).

FDA will sample shrimp products to determine their sulfite content. In measuring the level of sulfites in the shrimp, FDA will thaw and without further washing or rinsing analyze the shrimp for the presence of sulfiting agents using the method described in the 13th edition of the "Official Methods of Analysis of the Association of Official Analytical Chemists" in sections 20.106 through 20.108.

In addition, to ensure that there is proper labeling, FDA is advising the shrimp industry that shrimp products in package form that have been treated with sulfites must bear labeling that declares the presence of these substances as preservatives. Without such labeling, these products are misbranded.

FDA is prepared to take appropriate regulatory action if the shrimp industry fails to take action to ensure that residual sulfites are present only at CGMP levels, and that the presence of sulfiting agents as preservatives is declared on the label of shrimp products in packaged form.

The agency is issuing letters to the appropriate trade associations to ensure that they are aware of the matters contained in this notice.

Dated: January 15, 1985.

Joseph P. Hile,

Associate Commissioner for Regulatory Affairs.

[FR Doc. 85-1743 Filed 1-22-85; 8:45 am]

BILLING CODE 4160-01-M

ENVIRONMENTAL PROTECTION AGENCY

21 CFR Parts 193 and 561

[OPP-260050; FRL-2759-7]

Food for Human Consumption; Tolerances for Pesticides in Food Administered by the Environmental Protection Agency; and Animal Drugs, Feeds, and Related Products; Animal Feeds Administered by the Environmental Protection Agency; Cross-Reference Update

AGENCY: Environmental Protection Agency (EPA).

ACTION: Rule; Cross-Referencing Update.

SUMMARY: These editorial amendments to 21 CFR Parts 193 and 561 update cross-references to certain sections in 21 CFR Part 121 which was recodified, and Part 123 which was redesignated.

EFFECTIVE DATE: January 23, 1985.

FOR FURTHER INFORMATION CONTACT: John A. Richards, Chief, Federal Register Staff (TS-788), Office of the Assistant Administrator for Pesticides and Toxic Substances, Environmental Protection Agency, Rm. E-603A, 401 M Street SW., Washington, D.C. 20460, (202-382-3415).

SUPPLEMENTARY INFORMATION: The Food and Drug Administration (FDA) issued a recodification of 21 CFR Part 121, Subpart B—Exemption of Certain Food Additives from the Requirement of Tolerances; Subpart C—Food Additives Permitted in Feed and Drinking Water of Animals, published in **Federal Register** of September 10, 1976 (41 FR 38618). FDA issued a recodification of 21 CFR Part 121, Subpart D—Food Additives Permitted in Food for Human Consumption, published in the **Federal Register** of March 16, 1977 (42 FR 14302). In the **Federal Register** of June 28, 1976 (41 FR 26568), 21 CFR Part 123 was redesignated as 21 CFR Part 193.

These regulations are cross-referenced in 21 CFR Parts 193 and 561. This document amends the cross-references to reflect the new codification and/or redesignation under 21 CFR, and represents no substantive change in the contents of the regulations under CFR Parts 193 and 561.

List of Subjects in CFR Parts 193 and 561

Food additives, Feed additives, Pesticides and pests.

Dated: January 10, 1985.

Steven Schatzow,

Director, Office of Pesticide Programs.

Therefore, 21 CFR, Chapter I, is amended as follows:

PART 193—[AMENDED]

1. In Part 193, the following sections are amended as follows:

§ 193.200 [Amended]

a. In § 193.200(a), the reference to "§ 121.1209(a)" is changed to read "§ 173.355".

§ 193.250 [Amended]

b. In § 193.250(c), the reference to "§ 121.1194" is changed to read "§ 173.730(a)(2)".

§ 193.360 [Amended]

c. In § 193.360 (b) and (c)(3), the reference to "§ 123.320" is changed to read "§ 178.3730".

§ 193.520 [Amended]

d. In § 193.520, the reference to "§ 123.260" is changed to read "§ 193.260".

PART 561—[AMENDED]

§ 1561.365 [Amended]

2. In § 561.365, the reference to "§ 121.1154" (a) and (b)" is changed to read "§ 172.882 (a) and (b)".

(Sec. 409, 72 Stat. 1785 (21 U.S.C. 348))

[FR Doc. 85-1578 Filed 1-22-85; 8:45 am]

BILLING CODE 6560-50-M

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Parts 1 and 31

[T.D. 8006]

Income Tax; Taxable Years Beginning After December 31, 1953; Employment Taxes and Collection of Income Tax at Source; Income From Sources Without the United States Citizens or Residents of the United States Living Abroad

AGENCY: Internal Revenue Service, Treasury.

ACTION: Final regulations.

SUMMARY: This document contains final regulations relating to the treatment of income earned abroad by citizens or residents of the United States. Changes to the applicable tax law were made by the Economic Recovery Tax Act of 1981 and the Deficit Reduction Act of 1984. The regulations provide the public with guidance needed to comply with those acts.

DATES: The amendments are effective for taxable years beginning after December 31, 1981.

FOR FURTHER INFORMATION CONTACT: David J. Dean of the Legislation and Regulations Division, Office of Chief Counsel, Internal Revenue Service, 1111 Constitution Ave., NW., Washington, D.C. 20224 (Attention: CC:LR:T) 202-566-3289, not a toll-free call.

SUPPLEMENTARY INFORMATION:

Background

On July 20, 1983, the **Federal Register** published proposed amendments to the Income Tax Regulations (26 CFR Part 1) and Employment Tax Regulations (26 CFR Part 31) under sections 119, 911, and 3401 of the Internal Revenue Code of 1954 (48 FR 33007). The amendments were proposed to conform the regulations to changes made to the Internal Revenue Code by Sections 111, 112, and 113 of the Economic Recovery Tax Act of 1981 (Pub. L. 97-34, 95 Stat. 190, 196). A public hearing was held on November 15, 1983. After consideration of all comments received regarding the proposed amendments, those amendments are adopted as revised by this Treasury decision.

Discussion of Comments and Revised Amendments

Section 1.119-1 Meals and lodging furnished for the convenience of the employer.

Commentors proposed that the term "remote area" in paragraph (d)(1) should be defined to include any area where the standard of living is markedly lower than that prevailing in the United States and which is some distance from an area having a standard of living generally comparable to that prevailing in the United States. Such a definition would be too broad because it would include many cities, and would also raise the problem of defining the standard of living prevailing in the United States as well as in other places. The determination of what is a remote area must be based on the particular facts and circumstances and does not lend itself to specific definition; therefore, these regulations do not define that term. The Internal Revenue Service is considering the feasibility of designating certain areas as remote areas. The regulations have been changed to follow the statute more closely in using the term "place at which the employee renders services" instead of the term "Worksite."

Paragraph (d)(2) has been added to provide guidance in determining what constitutes satisfactory housing. One commentor suggested that the regulations establish a presumption that no satisfactory housing is available if the worksite is not within a reasonable commuting distance of 50,000 or more individuals. As there is no reasonable basis for this presumption, the proposal has not been adopted.

Paragraph (d)(3)(ii) establishes presumptions that satisfactory housing is unavailable if the employer is required to provide housing by a foreign government or an unrelated client. Some commentors suggested that the condition that such a requirement not be limited primarily to U.S. employers or employees should be dropped. Dropping this condition would encourage discriminatory treatment of U.S. employers or employees. For that reason, this suggestion has not been adopted. One commentor also suggested that the regulations should state that availability of housing to an employer does not necessarily mean that housing is available to the employee (the employer may be able to lease or buy a group of housing units that are not available individually). While this statement is correct, it is not necessary to include such a provision in the regulations because the test used by the regulations is whether satisfactory housing is available to the employee, rather than the employer, and the determination is based on facts and circumstances that are primarily relevant to the employee's ability to obtain satisfactory housing on the open market.

Two comments proposed that reasonable commuting distance, in paragraph (d)(3), should be limited to one hour's travel, as in previous regulations under section 913. In many areas of the United States and other countries commuters regularly travel more than one hour to or from work; accordingly, the regulations do not presume that commuting time in excess of one hour is unreasonable. Paragraph (d)(4) has been clarified, however, to insure that travel time is recognized as one factor to be considered in determining reasonable commuting distance. Paragraph (e) is also revised to clarify that the exclusion provided by section 119 applies to meals and lodging provided in kind on behalf of an employer to his employee.

Section 1.911-2 Qualified individuals.

Paragraph (a)(1) of § 1.911-2 (as well as § 1.911-3(d)(3)) has been revised to clarify that an individual must maintain a tax home in a foreign country during the 330 days of physical presence rather than the twelve month period with which the 330 days of physical presence must occur. Several comments expressed concern that this tax home requirement, in combination with Rev. Rul. 83-82, 1983-1 C.B. 45, may make it very difficult for individuals who are abroad for less than two years to qualify to make elections under section 911(d)(1)(B). The commentors proposed that the regulations require only that the tax home be maintained in a foreign country for some period less than the entire period of physical presence. The regulations do not adopt this approach because it is believed to be contrary to the intent of the statute in requiring both a tax home and physical presence in a foreign country. In addition, requiring the individual to maintain a tax home in a foreign country for some lesser period will not help those individuals who do not establish a tax home in a foreign country because they are present for less than two years.

A sentence has been added to paragraph (b) to clarify that an individual's abode is not necessarily in the United States, for purposes of the tax home requirement, merely because

the individual maintains a dwelling in the United States, such as a home for his family or an apartment used during business trips. Paragraph (d)(2) has been revised to provide that, for purposes of presence in a foreign country or countries, a person who is in transit between two points outside the United States may be physically present in the United States for less than twenty-four hours without being treated as present in the United States during such transit. This will permit most travel between foreign countries to be counted toward presence in a foreign country or countries even if, for example, it is between Canada and Mexico on an airplane that flies over or stops in the United States. However, proposals that travel days to and from the United States should be counted, in full or in part, as days of presence in a foreign country have not been adopted because they are not full days in a foreign country or countries, as required by section 911(d)(1)(B).

A suggestion that the regulations should provide for a waiver of the time requirements for becoming a qualified individual under circumstances such as illness of the individual or his spouse or dependents has not been adopted. The statute establishes specific time periods for qualification and specifically waives those time periods in certain cases of war, civil unrest, or similar adverse conditions requiring the individual to leave a foreign country. The statute does not provide authority to grant waivers of the time requirements in other cases.

Paragraph (e) of § 1.911–2 has been revised to clarify that a nonresident alien individual who makes an election under section 6013 (g) or (h) is entitled to use section 911 as a resident of the United States.

Section 1.911–3 Determination of amount of foreign earned income to be excluded.

The proposed regulations did not address the order in which foreign earned income received in years other than the year earned can be applied to the unused exclusion for the year in which the income was earned. Paragraph (e)(2) of § 1.911–3 has been added to clarify the order in which the exclusion is to be used. Income received in the year earned is applied first to the exclusion, and income received in other years may be applied, on a year by year basis, in any order the individual chooses.

One comment proposed that overseas allowances and reimbursements should be entirely foreign source, rather than allocated to U.S. or foreign source, rather than under the rules of § 1.861–4. The rationale provided was that these amounts are paid solely to compensate the individual for increased costs or inconvenience in connection with foreign assignment. This proposal was not adopted because such a rule would conflict with general principles of sourcing of income, and would create opportunities for abuse. Additionally, the rationale given is insufficient to support the proposal because increased costs and inconvenience to the taxpayer may result from working in more than one place (i.e. the United States and other countries) and in such a case they are attributable to all the places where work is performed.

A suggestion that salaries and wages received by cash basis taxpayers for the year-end payroll should be attributed to the year of receipt, for ease of administration, has been adopted. Such payroll payments are to be attributed entirely to the year in which they are received. However, a proposal to allow tax equalization payments to be attributed to the year of receipt has not been adopted. Such payments are often very large relative to an individual's salary. Because of the large amounts involved, this in not an appropriate area in which to allow administrative convenience to override the statutory requirement that income be attributed to the year in which services are performed for purposes of determining the amount of foreign earned income that may be excluded.

Commentors suggested that taxpayers be allowed to exclude amounts paid as compensation for future services in the year of receipt, subject to recapture in later years if it is determined that the individual was not entitled to the claimed exclusion. While such a rule would possibly reduce the need for amended returns and would reduce the potential for losing an exclusion due to the running of the statute of limitations, it would also greatly increase the administrative burden of determining whether a claimed exclusion was justified and whether the proper amount was excluded. It would also require adjustments in later years for recapture of improperly excluded amounts, would create a potential for recaptured amounts to be subject to lower tax rates than they would be subject to in the year of receipt, and may allow deferral or avoidance of tax, unless complex recapture provisions were developed. Because of the great potential for abuse and unnecessary complexity that such a rule would create, the suggestion is not incorporated into these regulations.

Examples have been added in paragraph (e)(4)(ii) to provide additional guidance in attributing bonuses to all of the services giving rise to that income and to clarify that bonuses are attributable on the basis of all the facts and circumstances. Comments indicated that the proposed rules appeared to some readers to attribute bonuses on a flat pro rata basis; this was not intended.

Paragraph (e)(5), dealing with moving expenses reimbursements, has been revised in several ways. The rules for determining the source of reimbursements have been expanded to provide more guidance with respect to the circumstance in which a written agreement or statement of company policy will be considered as evidence that a reimbursement for expenses of a return move to the United States is attributable to prior services performed in a foreign country (and thus is eligible for exclusion). Commentors suggested that oral agreements should be acceptable for this purpose, and also that the requirement of a written agreement should not be applied retroactively. Neither of these suggestions has been adopted.

Many comments suggested changes to the rules for allocating moving expense reimbursements to taxable years in which services giving rise to the reimbursements are performed. While the regulations have not adopted any of the proposals that would allow income to be excluded before an individual qualifies under the rules of § 1.911–2, the allocation rules for foreign source moving expense reimbursements have been modified. For moves beginning after December 31, 1983, reimbursements are considered attributable to services performed in the year of the move if the individual qualifies for a period that includes 120 days in the year of the move. If the individual's qualifying period does not include 120 days in the year of the move, the reimbursement is considered to be attributable to services performed in both the year of the move and the succeeding taxable year (or prior taxable year if the move is from a foreign country to the United States). Suggestions to allocate the reimbursements over a longer period of time when a longer period of employment is required by the employer for payment of a reimbursement were believed to add unnecessary complexity. The allocation rules apply regardless of the year in which the reimbursement is actually received. Examples have been added in paragraph (f), to demonstrate this moving expense reimbursement rule.

For moves beginning before January 1, 1984, the final regulations adopt the

moving expense reimbursement allocation rule that appeared in the proposed regulations. Under this rule, the reimbursement generally is allocated to services performed during the 12 month period following the move, which will usually span two taxable years. While this rule is more complex than the rule for moves after 1983, many taxpayers have filed returns for 1982 and 1983 using the proposed rule. By keeping that rule for moves before 1984, the final regulations permit those taxpayers to rely on the returns they have already filed, rather than requiring them to file amended returns to apply the new rule.

A special source rule is provided in paragraph (e)(5)(i) for storage expenses, which are incurred (and usually reimbursement) over a period of time approximately the same as the period during which services are performed. Thus, reimbursements for storage expenses are considered attributable to services performed during the time the expenses are incurred. This rule applies for expenses incurred after December 31, 1983.

Section 1.911–4 Determination of housing cost amount eligible for exclusion or deduction.

One commentor suggested that final regulations differentiate between repairs, which are includable housing expenses, and improvements, which are not includable housing expenses. The regulations do not elaborate on this issue because the determination of whether an expense is a repair or an improvement is controlled by the same principles that apply for purposes of section 162 and § 1.162–4, dealing with deductibility of trade or business expenses. Case law and rulings dealing with this issue under section 162 may provide guidance in specific cases.

Many comments suggested additional items for inclusion as housing expenses, such as local telephone charges, residential parking, cable television, and domestic labor. These regulations include residential parking as a housing expense because of the difficulty and inequity of differentiating between housing that includes parking and housing that does not. The other suggested items have not been included because they are almost always separate charges and are more in the nature of expenses of living which, like food, laundry, and entertainment, are not necessarily related to housing.

One commentor suggested that the final regulations define the terms "lavish or extravagant under the circumstances" and "the closest relationship not necessarily geographic". This suggestion was not adopted because these terms require, because of their nature, factual determinations.

A proposal to permit an individual to compute his base housing amount based on the number of qualifying days in the taxable year less the number of days that the individual excluded his lodging under section 119 was rejected. This proposal was rejected because the statute clearly requires that an individual's base housing amount be determined based on the total number of his qualifying days in the taxable year.

Commentors criticized the definition of employer provided amounts because under the definition provided in § 1.911–4(d)(2) an employee cannot have foreign earned income that is not an employer provided amount. Commentors think that employees may bear housing costs out of capital or other income, and, in that case, should be entitled to a deduction. Commentors also suggest that an individual may, in effect, claim a double benefit if the housing cost amount is deductible rather than excludable because section 911(d)(6), which disallows double benefits, does not apply to deductible amounts. These arguments were rejected for the following reasons. First, under section 911(d)(7) the sum of amounts excluded under section 911(a) and the amount deducted under section 911(c)(3)(A) may not exceed the individual's foreign earned income for the year. Thus, if an employee actually bears housing costs out of capital or income that is not foreign earned income the employee is not entitled to a deduction; the deduction and exclusions are limited by the amount of foreign earned income for the year. Second, by defining all amounts that an employer pays to or on behalf of an employee as employer provided amounts, the regulations avoid the confusion and complexity that would be associated with determining whether an amount was employer provided or non-employer provided based on the form in which it was received. Third, the commentors' suggestion that double benefits attributable to deductible housing cost amounts are allowable is incorrect. Section 1.911–6(c)(1) provides that, for purposes of determining the extent to which foreign taxes are disallowed, the housing cost amount deduction is treated as definitely related to foreign earned income that is not excluded. This rule is in accord with the regulations under § 1.861–8 which allocate deductions to the class of income to which they are related.

A commentor suggested that the formula for dividing the housing cost amount between employer provided amounts and non-employer provided amounts may not be appropriate in cases where the individual is self-employed for part of a year and an employee for part of a year. However, the alternative suggested, a facts and circumstances test, would not provide adequate guidance and would be too complex to be workable.

Section 1.911–5 Special rules for married couples.

A suggestion that spouses should compute only one base housing amount is partially incorporated into the regulations by allowing spouses to allocate all their housing expenses to one of them if they reside together, even if they file separate returns. However, spouses residing apart must compute their housing cost amounts separately, and must use a separate base housing amount for each spouse who excludes or deducts a housing cost amount.

The formula for dividing the housing cost amount between employer provided amounts (excludable) and non-employer provided amounts (deductible) is computed separately by each spouse claiming a housing cost amount, based on his or her separate foreign earned income.

Section 1.911–6 Disallowance of deductions, exclusions, and credits.

One comment raised the question of whether employee income and self-employment income must be pooled for purposes of determining the amount excluded and the disallowance of deductions. Because there is no differentiation, for exclusion purposes, between these two categories of income, an individual who has foreign earned income in excess of the amount he elects to exclude is considered to have excluded a pro rate portion of employee and self-employment income. Thus, a pro rate portion of deductions attributable to the self-employment income will be disallowed, and the individual is not permitted to allocate his employee income to excluded amounts and his self-employment income to non-excluded amounts. The regulations accomplish this in the rules of paragraph (a) by allocating and apportioning deductions first to foreign earned income and U.S. source earned income, and then, within foreign earned income, to excluded and non-excluded amounts.

One commentor suggested that deductions for qualified retirement contributions should be allocated to U.S. source income, for purposes of disallowance of deductions, because the qualified retirement plan generates U.S.

source income. This suggestion was not adopted because the deduction is limited by and attributable to compensation includible in the individual's gross income for purposes of determining the allowability, and source, of the deduction.

Many commentors criticized the proposed allocation of a moving expense deduction for a return move to the United States to foreign earned income if a reimbursement received for the same move is treated as foreign source under § 1.911–3. The proposed regulations matched the deduction to the reimbursement because they both arise from the same move and are therefore related. Since the reimbursement is used as an inducement to work abroad, it is related to that work and also makes the expenses that are reimbursed related to that work. For these reasons, the final regulations retain the rule requiring the deduction to be allocated to the same source as the reimbursement.

Comments also suggested that the denominator of the fraction used for disallowance of the moving expense deduction (for a move to a foreign country) should include all earned income rather than only foreign earned income. This suggestion has not been adopted because the deduction is more properly related to the new principal place of business, which will produce foreign earned income, rather than to all sources of income earned after the move. Suggestions were also made to limit the foreign earned income denominator of the fraction to foreign earned income received in the year or years to which the deduction is attributable. While this rule would eliminate the need for amended returns in some cases and thereby reduce complexity in this area, the rule would always work to the disadvantage of individuals wishing to file amended returns on which they could claim a larger moving expense deduction. Therefore, the suggestion was not adopted.

Several comments stated that the rule for attributing a moving expense deduction to the year of the move or to that year and the following year was too confusing and complex. In response to these comments, the rule has been changed, for moves beginning after December 31, 1983, to allow the deduction to be attributed entirely to the year of the move if the individual is a qualified individual for a period that includes 120 days in the year of the move (rather than requiring the individual to be a qualified individual for the entire taxable year). If the individual cannot attribute the deduction entirely to the year of the move under this rule, the deduction is attributed to that year and the entire following year. The new rule will allow many individuals (those who qualify for 120 days or more in the year of the move) to determine the amount of their moving expense deduction without having to allocate the deduction over two years and without amending their returns or recapturing amounts deducted that are subsequently disallowed. Individuals who do not qualify for 120 days in the year of the move may deduct their moving expenses in the year of the move, to the extent the expenses are not attributable to income excluded in that year. If the individuals exclude income in the next year, a portion of the deductions will be disallowed and the individuals must then either file amended returns or include that amount in income for the following year as income other than foreign earned income.

For moves beginning before January 1, 1984, the rule has been adopted as it appeared in the proposed regulations. This eliminates the necessity of filing amended returns for those individuals who have filed 1982 or 1983 returns using the proposesd rule.

Suggestions to provide a rule attributing storage expenses to the period of time when they are incurred have been incorporated into the regulations, effective for expenses incurred after December 31, 1983. Thus, to the extent that such expenses are deductible under section 217, they will be subject to disallowance based on the formula provided, as applied to the year in which the expenses are incurred. These moving and storage expense attribution rules parallel the treatment of income from reimbursements for these expenses under § 1.911–3.

Several comments related to the disallowance formula for deductible or creditable foreign taxes. A few comments proposed that the denominator of the disallowance fraction should include all income subject to foreign tax, regardless of character or source. Paragraph (c)(1) of § 1.911–6 states that the determination of the amount to be disallowed must begin with the foreign taxes imposed on foreign earned income. Recognizing that it is not always possible to segregate the foreign taxes imposed on foreign earned income and those imposed on other income, the last sentence of paragraph (c)(1) provides that the denominator of the disallowance fraction may include other amounts of income subject to foreign tax. This matches the tax with the amounts on which it is imposed, so that taxes on income other than excluded income will not be disallowed. This did not require any change from the proposed regulations. Paragraph (c)(1) has been changed somewhat, however, to clarify that all of the amounts used in the disallowance formula are amounts received, accrued, or excluded in the taxable year, rather than amounts relating to the exclusion limitation for the taxable year. This will help to ensure that the disallowance formula relates to amounts subject to foreign tax in that year.

Commentors also noted that the proposed regulations did not provide rules for determining the portion of foreign taxes disallowed if the foreign jurisdiction uses a fiscal taxable year. They suggested that the foreign taxes should accrue on a pro rata basis over the course of the year and should be allocated to income earned in the year that the taxes are considered accrued. This suggestion has been adopted in paragraph (c)(2), along with a definition of taxable year for this purpose and a rule to clarify that the effect of disallowance is to reduce the amount of foreign taxes eligible for deduction or credit without affecting the time for claiming such deduction or credit.

A few commentors suggested that allocation of the housing cost amount deduction to foreign earned income that is not excluded (under paragraph (a)) produces an incorrect result because, under paragraph (c), it reduces the denominator of the foreign tax disallowance fraction, thus disallowing foreign taxes on that amount to the extent that it decreases the size of the denominator relative to the numerator of the fraction. The commentors suggested that section 911(d)(7), which disallows double benefits, does not apply amounts deducted under section 911(c)(3)(A). The regulations do not adopt this interpretation of the statute.

Section 1.911–6(a) of the regulations provides, for purposes of determining the allowable housing cost amount deduction, no portion of the deduction is allocated to amounts excluded under section 911(a). The housing cost amount deduction is allowed, however, only to the extent of the excess of foreign earned income over excluded foreign earned income. Therefore, it is appropriate to allocate the housing cost amount deduction, in full, to foreign earned income that is not excluded.

One commentor suggested that the housing cost amount deduction should only reduce the denominator of the disallowance fraction if the foreign jurisdiction allows the deduction. The problem with this approach is that it

fails to recognize that the concepts of foreign earned income and deductions allocable to foreign earned income are defined under U.S. law. Finally, because the housing cost amount deduction reduces taxable income for U.S. tax purposes (as does the housing cost amount exclusion), but is not included in the numerator of the disallowance fraction as a positive amount (while the housing cost amount exclusion is), it must reduce the denominator of the fraction or it will not affect the disallowance. If it does not affect the disallowance, a credit or deduction will ultimately be allowed for taxes imposed on income that is not subject to U.S. taxation. The purpose of the foreign tax credit or deduction is to offset U.S. tax on income subject to tax in both the United States and a foreign country, and this amount of income is not subject to tax in the United States. Therefore, this deduction must reduce the denominator of the disallowance fraction.

Two comments asserted that an inequitable result is obtained in the case of the sole proprietorship by basing the disallowance of deductions on gross income rather than net income, because deductions are thus partially disallowed that would not enter into the individual's computation of gross income if the business were operated as a corporation. One commentor suggested that the statute could be interpreted in such a way as to allow the regulations to use a net income approach in the sole proprietorship context. The other commentor agrees that the approach used in the proposed regulations is required by the statutory language and believes the statute should be changed. The final regulations retain the gross income approach because it is required by the statute and is consistent with the longstanding administrative interpretation of the statutory language. This language has remained consistent throughout major changes made to section 911.

Section 1.911–7 Procedural rules.

The proposed regulations contained a requirement that an election to claim section 911 exclusions be made on a timely filed return. Many commentors criticized this rule as being unduly harsh, citing the many problems individuals may encounter in trying to file timely returns, such as poor or slow mail service from foreign countries, busy travel schedules, and difficulty obtaining forms and information. The final regulations contain a modified filing requirement. A qualified individual may make a valid election on a timely filed return, a return amending a timely filed return, or a first return filed within one year from the original due date of the return. This one year grace period does not constitute extension of time for any purpose; it is merely a period during which a valid election may be made with an income tax return that is filed late. The final regulations also provide a period of six months from the date of publication for making a valid election for a taxable year beginning before January 1, 1984.

Paragraph (a)(4) has also been added to provide that an inadvertent error or omission of information will not invalidate an election if the error is relatively insignificant.

Several comments proposed that individuals should be allowed to revoke an election for the first taxable year for which it is made, or to file an amended return for that year, on which the election is not made, which would not be considered a revocation. The rules for making a revocation of an election, contained in paragraph (b)(1) of § 1.911–7, have been changed to allow an election to be revoked for the first taxable year for which it was made, but such a revocation will be treated the same as a revocation for any other year, and consent will be required to reelect within 5 years therafter.

Paragraph (b)(2), relating to reelections during the period when consent to reelect is required, has been changed to add two additional factors to be considered in determining whether consent will be given. Comments suggesting that the regulations provide additional guidance on circumstances to be considered favorably or unfavorably in determining whether consent will be given to reelect after a revocation have not been followed because many facts or circumstances could be favorable in some situations and unfavorable in other situations.

A suggestion that individuals be allowed to file requests for extensions with U.S. embassies has not been adopted because such requests are not considered or granted by officials in U.S. embassies, and embassies are not generally involved with tax administration.

Section 31.3401(a)(8)(A)–1 Remuneration for services performed outside the United States by citizens of the United States

One commentor noted that the method of exemption from withholding used in the proposed regulations would result in overwithholding in most cases in which any amounts were required to be withheld. The final regulations have adopted the suggested solution for payments made after December 31, 1984. The final regulations provide, in paragraph (a)(1)(ii), that a pro rata portion of each pay period's salary is exempt from withholding, instead of exempting all amounts paid until the excludable amount has been reached and then withholding on all subsequent amounts paid.

Executive Order 12291 and Regulatory Flexibility Act

The Commissioner of Internal Revenue has determined that these regulations are not major regulations as defined in Executive Order 12291 and therefore a regulatory impact analysis is not required. The Internal Revenue Service has concluded that these regulations are interpretative and thus the notice and public comment procedure requirements of 5 U.S.C. 553 do not apply. Accordingly, these regulations do not constitute regulations subject to the Regulatory Flexibility Act (5 U.S.C. Chapter 6).

Paperwork Reduction Act of 1980

The collection of information requirements contained in this regulations have been submitted to the Office of Management and Budget (OMB) in accordance with the requirements of the Paperwork Reduction Act of 1980. These requirement have been approved under OMB number 1545–0067.

Drafting Information

The principal author of this regulation is David J. Dean of the Legislation and Regulations Division of the Office of Chief Counsel, Internal Revenue Service. However, personnel from other offices of the Internal Revenue Service and Treasury Department participated in developing the regulations on matters of substance and style.

List of Subjects

26 CFR 1.61 Through 1.281–4

Income taxes, Taxable income, Deductions, Exemptions.

26 CFR 1.861–1 Through 1.997–1

Income taxes, Aliens, Exports, DISC, Foreign investments in U.S., Foreign tax credit, Sources of income, United States investment abroad.

26 CFR Part 31

Employment taxes, Income taxes, Lotteries, Railroad retirement, Social security, Unemployment tax, Withholding.

Adoption of Amendments to the Regulations

According, 26 CFR Parts 1 and 31 are amended as follows:

Income Tax Regulations

Paragraph 1. Section 1.119–1 is amended by revising paragraph (c), by redesignating paragraph (d) as paragraph (f), and by adding paragraphs (d) and (e). The revised and added paragraphs read as follows:

§ 1.119–1 Meals and lodging furnished for the convenience of the employer.

* * * * *

(c) *Business premises of the employer*—(1) *In general.* For purposes of this section, the term "business premises of the employer" generally means the place of employment of the employee. For example, meals and lodging furnished in the employer's home to a domestic servant would constitute meals and lodging furnished on the business premises of the employer. Similarly, meals furnished to cowhands while herding their employer's cattle on leased land would be regarded as furnished on the business premises of the employer.

(2) *Certain camps.* For taxable years beginning after December 31, 1981, in the case of an individual who is furnished lodging by or on behalf of his employer in a camp (as defined in paragraph (d) of this section) in a foreign country (as defined in § 1.911–2(h)), the camp shall be considered to be part of the business premises of the employer.

(d) *Camp defined*—(1) *In general.* For the purposes of paragraph (c)(2) of this section, a camp is lodging that is all of the following:

(i) Provided by or on behalf of the employer for the convenience of the employer because the place at which the employee renders services is in a remote area where satisfactory housing is not available to the employee on the open market within a reasonable commuting distance of that place;

(ii) Located, as near as practicable, in the vicinity of the place at which the employee renders services; and

(iii) Furnished in a common area or enclave which is not available to the general public for lodging or accommodations and which normally accommodates ten or more employees.

(2) *Satisfactory housing.* For purposes of paragraph (d)(1)(i) of this section, facts and circumstances that may be relevant in determining whether housing available to the employee is satisfactory include, but are not limited to, the size and condition of living space and the availability and quality of utilities such as water, sewers or other waste disposal facilities, electricity, or heat. The general environment in which housing is located (*e.g.* climate, prevalence of insects, etc.) does not of itself make housing unsatisfactory. The general environment is relevant, however, if housing is inadequate to protect the occupants from environmental conditions. The individual employee's income level is not relevant in determining whether housing is satisfactory; it may, however, be relevant in determining whether satisfactory housing is available to the employee (see paragraph (d)(3)(i)(B) of this section).

(3) *Availability of satisfactory housing*—(i) *Facts and circumstances.* For purposes of paragraph (d)(1)(i) of this section, facts and circumstances to be considered in determining whether satisfactory housing is available to the employee on the open market include but are not limited to:

(A) The number of housing units available on the open market in relation to the number of housing units required for the employer's employees;

(B) The cost of housing available on the open market;

(C) The quality of housing available on the open market; and

(D) The presence of warfare or civil insurrection within the area where housing would be available which would subject U.S. citizens to unusual risk of personal harm or property loss.

(ii) *Presumptions.* Satisfactory housing will generally be considered to be unavailable to the employee on the open market if either of the following conditions is satisfied:

(A) The foreign government requires the employer to provide housing for its employees other than housing available on the open market; or

(B) An unrelated person awarding work to the employer requires that the employer's employees occupy housing specified by such unrelated person.

The condition of either paragraph (d)(3)(ii) (A) or (B) of this section is not satisfied if the requirement described therein and imposed either by a foreign government or unrelated person applies primarily to U.S. employers and not to a significant number of third country employers or applies primarily to employers of U.S. employees and not to a significant number of employers of third country employees.

(4) *Reasonable commuting distance.* For purposes of paragraph (d)(1)(i) of this section, in determining whether a commuting distance is reasonable, the accessibility of the place at which the employee renders services due to geographic factors, the quality of the roads, the customarily available transportation, and the usual travel time (at the time of day such travel would be required) to the place at which the employee renders services shall be taken into account.

(5) *Common area or enclave.* A cluster of housing units does not satisfy paragraph (d)(1)(iii) of this section if it is adjacent to or surrounded by substantially similar housing available to the general public. Two or more common areas or enclaves that house employees who work on the same project (for example, a highway project) are considered to be one common area or enclave in determining whether they normally accommodate ten or more employees.

(e) *Rules.* The exclusion provided by section 119 applies only to meals and lodging furnished in kind by or on behalf of an employer to his employee. If the employee has an option to receive additional compensation in lieu of meals or lodging in kind, the value of such meals and lodging is not excludable from gross income under section 119. However, the mere fact that an employee, at his option, may decline to accept meals tendered in kind will not of itself require inclusion of the value thereof in gross income. Cash allowances for meals or lodging received by an employee are includible in gross income to the extent that such allowances constitute compensation.

* * * * *

Par. 2. Sections 1.911–1 through 1.911–7 are removed and new §§ 1.911–1 through 1.911–8 are added to read as follows:

§ 1.911–1 Partial exclusion for earned income from sources within a foreign country and foreign housing costs.

(a) *In general.* Section 911 provides that a qualified individual may elect to exclude the individual's foreign earned income and the housing cost amount from the individual's gross income for the taxable year. Foreign earned income is excludable to the extent of the applicable limitation for the taxable year. The housing cost amount for the taxable year is excludable to the extent attributable to employer provided amounts. If a portion of the housing cost amount for the taxable year is attributable to non-employer provided amounts, such amount may be deductible by the qualified individual subject to a limitation. The amounts excluded under section 911(a) and the amount deducted under section 911(c)(3)(A) for the taxable year shall not exceed the individual's foreign earned income for such taxable year. Foreign earned income must be earned during a period for which the individual qualifies to make an election under section 911(d)(1). A housing cost amount

that would be deductible except for the application of this limitation may be carried over to the next taxable year and is deductible to the extent of the limitation for that year. Except as otherwise provided, §§ 1.911–1 through 1.911–7 apply to taxable years beginning after December 31, 1981. These sections do not apply to any item of income, expense, deduction, or credit arising before January 1, 1982, even if such item is attributable to services performed after December 31, 1981.

(b) *Scope.* Section 1.911–2 provides rules for determining whether an individual qualifies to make an election under section 911. Section 1.911–3 provides rules for determining the amount of foreign earned income that is excludable under section 911(a)(1). Section 1.911–4 provides rules for determining the housing cost amount and the portions excludable under section 911(a)(2) or deductible under section 911(c)(3). Section 1.911–5 provides special rules applicable to married couples. Section 1.911–6 provides for the disallowance of deductions, exclusions, and credits attributable to amounts excluded under section 911. Section 1.911–7 provides procedural rules for making or revoking an election under section 911.

Section 1.911–8 provides a reference to rules applicable to taxable years beginning before January 1, 1982.

§ 1.911–2 Qualified individuals.

(a) *In general.* An individual is a qualified individual if:

(1) The individual's tax home is in a foreign country or countries throughout—

(i) The period of bona fide residence described in paragraph (a)(2)(i) of this section, or

(ii) The 330 full days of presence described in paragraph (a)(2)(ii) of this section, and

(2) The individual is either—

(i) A citizen of the United States who establishes to the satisfaction of the Commissioner or his delegate that the individual has been a bona fide resident of a foreign country or countries for an uninterrupted period which includes an entire taxable year, or

(ii) A citizen or resident of the United States who has been physically present in a foreign country or countries for at least 330 full days during any period of twelve consecutive months.

(b) *Tax home.* For purposes of paragraph (a)(i) of this section, the term "tax home" has the same meaning which it has for purposes of section 162(a)(2) (relating to travel expenses away from home). Thus, under section 911, an individual's tax home is considered to be located at his regular or principal (if more than one regular) place of business or, if the individual has no regular or principal place of business because of the nature of the business, then at his regular place of abode in a real and substantial sense. An individual shall not, however, be considered to have a tax home in a foreign country for any period for which the individual's abode is in the United States. Temporary presence of the individual in the United States does not necessarily mean that the individual's abode is in the United States during that time. Maintenance of a dwelling in the United States by an individual, whether or not that dwelling is used by the individual's spouse and dependents, does not necessarily mean that the individual's abode is in the United States.

(c) *Determination of bona fide residence.* For purposes of paragraph (a)(2)(i) of this section, whether an individual is a bona fide resident of a foreign country shall be determined by applying, to the extent practical, the principles of section 871 and the regulations thereunder, relating to the determination of the residence of aliens. Bona fide residence in a foreign country or countries for an uninterrupted period may be established, even if temporary visits are made during the period to the United States or elsewhere on vacation or business. An individual with earned income from sources within a foreign country is not a bona fide resident of that country if:

(1) The individual claims to be a nonresident of that foreign country in a statement submitted to the authorities of that country, and

(2) The earned income of the individual is not subject, by reason of nonresidency in the foreign country, to the income tax of that country.

If an individual has submitted a statement of nonresidence to the authorities of a foreign country the accuracy of which has not been resolved as of any date when a determination of the individual's bona fide residence is being made, then the individual will not be considered a bona fide resident of the foreign country as of that date.

(d) *Determination of physical presence.* For purposes of paragraph (a)(2)(ii) of this section, the following rules apply.

(1) *Twelve-month test.* A period of twelve consecutive months may begin with any day but must end on the day before the corresponding day in the twelfth succeeding month. The twelve-month period may begin before or after arrival in a foreign country and may end before or after departure.

(2) *330-day test.* The 330 full days need not be consecutive but may be interrupted by periods during which the individual is not present in a foreign country. In computing the minimum 330 full days of presence in a foreign country or countries, all separate periods of such presence during the period of twelve consecutive months are aggregated. A full day is a continuous period of twenty-four hours beginning with midnight and ending with the following midnight. An individual who has been present in a foreign country and then travels over areas not within any foreign country for less than twenty-four hours shall not be deemed outside a foreign country during the period of travel. If an individual who is in transit between two points outside the United States is physically present in the United States for less than twenty-four hours, such individual shall not be treated as present in the United States during such transit but shall be treated as travelling over areas not within any foreign country. For purposes of this paragraph (d)(2), the term "transit between two points outside the United States" has the same meaning that it has when used in section 7701(b)(6)(C).

(3) *Illustrations of the physical presence requirement.* The physical presence requirement of paragraph (a)(2)(ii) of this section is illustrated by the following examples:

Example (1). B, a U.S. citizen, arrives in Venezuela from New York at 12 noon on April 24, 1982. B remains in Venezuela until 2 p.m. on March 21, 1983, at which time B departs for the United States. Among other possible twelve month periods, B is present in a foreign country an aggregate of 330 full days during each of the following twelve month periods: March 21, 1982 through March 20, 1983; and April 25, 1982 through April 24, 1983.

Example (2). C, a U.S. citizen, travels extensively from the time C leaves the United States on March 5, 1982, until the time C departs the United Kingdom on January 1, 1984, to return to the United States permanently. The schedule of C's travel and the number of full days at each location are listed below:

Country	Time and date of arrival	Time and date of departure	Full days in foreign country
United States		10 p.m. (by air) Mar. 5, 1982	
United Kingdom	9 a.m. Mar. 6, 1982	10 p.m. (by ship) June 25, 1982	110
United States	11 a.m. June 30, 1982	1 p.m. (by ship) July 19, 1982	0

Country	Time and date of arrival	Time and date of departure	Full days in foreign country
France	3 p.m. July 24, 1982	11 a.m. (by air) Aug. 22, 1983	393
United States	4 p.m. Aug. 22, 1983	9 a.m. (by air) Sept. 4, 1983	0
United Kingdom	9 a.m. Sept. 5, 1983	9 a.m. (by air) Jan 1, 1984	117
United States	1 p.m. Jan. 1, 1984		

Among other possible twelve month periods, C is present in a foreign country or countries an aggregate of 330 full days during the following twelve month periods: March 2, 1982 through March 1, 1983; and January 21, 1983 through January 20, 1984. The computation of days with respect to each twelve month period may be illustrated as follows:

First twelve month period (March 2, 1982 through March 1, 1983):

	Full days in foreign country
Mar. 2, 1982 through Mar. 6, 1982	0
Mar. 7, 1982 through June 24, 1982	110
June 25, 1982 through July 24, 1982	0
July 25, 1982 through Mar. 1, 1983	220
Total full days	330

Second twelve month period (January 21, 1983 through January 20, 1984):

	Full days in foreign country
Jan. 21, 1983 through Aug. 21, 1983	213
Aug. 22, 1983 through Sept. 5, 1983	0
Sept. 6, 1983 through Dec. 31, 1983	117
Jan. 1, 1984 through Jan. 20, 1984	0
Total full days	330

(e) *Special rules.* For purposes only of establishing that an individual is a qualified individual under paragraph (a) of this section, residence or presence in a foreign country while there employed by the U.S. government or any agency or instrumentality of the U.S. government counts towards satisfaction of the requirements of § 1.911–2(a). (But see section 911(b)(1)(B)(ii) and § 1.911–3(c)(3) for the rule excluding amounts paid by the U.S. government to an employee from the definition of foreign earned income.) Time spent in a foreign country prior to January 1, 1982, counts toward satisfaction of the bona fide residence and physical presence requirements, even though no exclusion or deduction may be allowed under section 911 for income attributable to services performed during that time. For purposes or paragraph (a)(2)(ii) of this section, the term "resident of the United States" includes an individual for whom a valid election is in effect under section 6013 (g) or (h) for the taxable year or years during which the physical presence requirement is satisfied.

(f) *Waiver of period of stay in foreign country due to war or civil unrest.* Notwithstanding the requirements of paragraph (a) of this section, an individual whose tax home is in, a foreign country, and who is a bona fide resident of, or present in a foreign country for any period, who leaves the foreign country after August 31, 1978, before meeting the requirements of paragraph (a) of this section, may as provided in this paragraph, qualify to make an election under section 911(a) and § 1.911–7(a). If the Secretary determines, after consultation with the Secretary of State or his delegate, that war, civil unrest, or similar adverse conditions existed in a foreign country, then the Secretary shall publish the name of the foreign country and the dates between which such conditions were deemed to exist. In order to qualify to make an election under this paragraph, the individual must establish to the satisfaction of the Secretary that the individual left a foreign country, the name of which has been published by the Secretary, during the period when adverse conditions existed and that the individual could reasonably have expected to meet the requirements of paragraph (a) of this section but for the adverse conditions. The individual shall attach to his return for the taxable year a statement that the individual expected to meet the requirements of paragraph (a) of this section but for the conditions in the foreign country which precluded the normal conduct of business by the individual. Such individual shall be treated as a qualified individual, but only for the actual period of residence or presence. Thus, in determining the number of the individual's qualifying days, only days within the period of actual residence or presence shall be counted.

(g) *United States.* The term "United States" when used in a geographical sense includes any territory under the sovereignty of the United States. It includes the states, the District of Columbia, the possessions and territories of the United States, the territorial waters of the United States, the air space over the United States, and the seabed and subsoil of those submarine areas which are adjacent to the territorial waters of the United States and over which the United States has exclusive rights, in accordance with international law, with respect to the exploration and exploitation of natural resources.

(h) *Foreign country.* The term "foreign country when used in a geographical sense includes any territory under the sovereignty of a government other than that of the United States. It includes the territorial waters of the foreign country (determined in accordance with the laws of the United States), the air space over the foreign country, and the seabed and subsoil of those submarine areas which are adjacent to the territorial waters of the foreign country and over which the foreign country has exclusive rights, in accordance with international law, with respect to the exploration and exploitation of natural resources.

§ 1.911–3 Determination of amount of foreign earned income to be excluded.

(a) *Definition of foreign earned income.* For purposes of section 911 and the regulations thereunder, the term "foreign earned income" means earned income (as defined in paragraph (b) of this section) from sources within a foreign country (as defined in § 1.911–2(h)) that is earned during a period for which the individual qualifies under § 1.911–2(a) to make an election. Earned income is from sources within a foreign country if it is attributable to services performed by an individual in a foreign country or countries. The place of receipt of earned income is immaterial in determining whether earned income is attributable to services performed in a foreign country or countries.

(b) *Definition of earned income*—(1) *In general.* The term "earned income" means wages, salaries, professional fees, and other amounts received as compensation for personal services actually rendered including the fair market value of all remuneration paid in any medium other than cash. Earned income does not include any portion of an amount paid by a corporation which represents a distribution of earnings and profits rather than a reasonable allowance as compensation for personal services actually rendered to the corporation.

(2) *Earned income from business in which capital is material.* In the case of an individual engaged in a trade or business (other than in corporate form) in which both personal services and capital are material income producing factors, a reasonable allowance as compensation for the personal services actually rendered by the individual shall be considered earned income, but the total amount which shall be treated as the earned income of the individual from such trade or business shall in no case exceed thirty percent of the individual's

share of the net profits of such trade or business.

(3) *Professional fees.* Earned income includes all fees received by an individual engaged in a professional occupation (such as doctor or lawyer) in the performance of professional activities. Professional fees constitute earned income even though the individual employs assistants to perform part or all of the services, provided the patients or clients are those of the individual and look to the individual as the person responsible for the services rendered.

(c) *Amounts not included in foreign earned income.* Foreign earned income does not include an amount:

(1) Excluded from gross income under section 119;

(2) Received as a pension or annuity (including social security benefits);

(3) Paid to an employee by an employer which is the U.S. government of any U.S. government agency or instrumentality;

(4) Included in the individual's gross income by reason of section 402(b) (relating to the taxability of a beneficiary of a nonexempt trust) or section 403(c) (relating to the taxability of a beneficiary under a nonqualified annuity or under annuities purchased by exempt organizations);

(5) Included in gross income by reason of § 1.911–6(b)(4)(ii); or

(6) Received after the close of the first taxable year following the taxable year in which the services giving rise to the amounts were performed. For treatment of amounts received after December 31, 1962, which are attributable to services performed on or before December 31, 1962, and with respect to which there existed on March 12, 1962, a right (whether forfeitable or nonforfeitable) to receive such amounts, see § 1.72–8.

(d) *Determination of the amount of foreign earned income that may be excluded under section 911(a)(1)*—(1) *In general.* Foreign earned income described in this section may be excluded under section 911(a)(1) and this paragraph only to the extent of the limitation specified in paragraph (d)(2) of this section. Income is considered to be earned in the taxable year in which the services giving rise to the income are performed. The determination of the amount of excluded earned income in this manner does not affect the time for reporting any amounts included in gross income.

(2) *Limitation*—(i) *In general.* The term "section 911(a)(1) limitation" means the amount of foreign earned income for a taxable year which may be excluded under section 911(a)(1). The section 911(a)(1) limitation shall be equal to the lesser of the qualified individual's foreign earned income for the taxable year in excess of amounts that the individual elected to exclude from gross income under section 911(a)(2) or the product of the annual rate for the taxable year (as specified in paragraph (d)(2)(ii) of this section) multiplied by the following fraction:

$$\frac{\text{The number of qualifying days in the taxable year}}{\text{The number of days in the taxable year}}$$

(ii) *Annual rate for the taxable year.* The annual rate for the taxable year is the rate set forth in section 911(b)(2)(A).

(3) *Number of qualifying days.* For purposes of section 911 and the regulations thereunder, the number of qualifying days is the number of days in the taxable year within the period during which the individual met the tax home requirement and either the bona fide residence requirement or the physical presence requirement of §1.911–2(a). Although the period of bona fide residence must include an entire taxable year, the entire uninterrupted period of residence may include fractional parts of a taxable year. For instance, if an individual who was a calendar year taxpayer established a tax home and a residence in a foreign country as of November 1, 1982, and maintained the tax home and the residence through March 31, 1984, then the uninterrupted period of bona fide residence includes fractional parts of the years 1982 and 1984, and all of 1983. The number of qualifying days in 1982 is sixty-one. The number of qualifying days in 1983 is 365. The number of qualifying days in 1984 is ninety-one. The period during which the physical presence requirement of §1.911–2(a)(2)(ii) is met is any twelve consecutive month period during which the individual is physically present in one or more foreign countries for 330 days and the indiyidual's tax home is in a foreign country during each day of such physical presence. Such period may include days when the individual is not physically present in a foreign country, and days when the individual does not maintain a tax home in a foreign country. Such period may include fractional parts of a taxable year. Thus, if an individual's period of physical presence is the twelve-month period beginning June 1, 1982, and ending May 31, 1983, the number of qualifying days in 1982 is 214 and the number of qualifying days in 1983 is 151.

(e) *Attribution rules*—(1) *In general.* Foreign earned income is considered to be earned in the taxable year in which the individual performed the services giving rise to the income. If income is earned in one taxable year and received in another taxable year, then, for purposes of determining the amount of foreign earned income that the individual may exclude under section 911(a), the individual must attribute the income to the taxable year in which the services giving rise to the income were performed. Thus, any reimbursement would be attributable to the taxable year in which the services giving rise to the obligation to pay the reimbursement were performed, not the taxable year in which the reimbursement was received. For example, tax equalization payments are normally received in the year after the year in which the services giving rise to the obligation to pay the tax equalization payment were performed. Therefore, such payments will almost always have to be attributed to the prior year. Foreign earned income attributable to services performed in a preceding taxable year shall be excludable from gross income in the year of receipt only to the extent such amount could have been excluded under paragraph (d)(1) in the preceding taxable year, had such amount been received in the preceding taxable year. The taxable year to which income is attributable will be determined on the basis of all the facts and circumstances.

(2) *Priority of use of the section 911(a)(1) limitation.* Foreign earned income received in the year in which it is earned shall be applied to the section 911(a)(1) limitation for that year before applying income earned in that year that is received in any other year. Foreign earned income that is earned in one year and received in another year shall be applied to the section 911(a)(1) limitation for the year in which it was earned, on a year by year basis, in any order that the individual chooses. (But see section 911(b)(1)(B)(iv)). An individual may not amend his return to change the treatment of income with respect to the section 911(a)(1) exclusion after the period provided by section 6511(a). The special period of limitation provided by section 6511(d)(3) does not apply for this purpose. For example, C, a qualified individual, receives an advance bonus of $10,000 in 1982, salary of $70,000 in 1983, and a performance bonus of $10,000 in 1984, all of which are foreign earned income for 1983. C has a section 911(a)(1) limitation for 1983 of $80,000, and has no housing cost amount exclusion. On his income tax return for 1983, C elects to exclude foreign earned income of $70,000 received in 1983. C may also exclude his $10,000 advance bonus received in 1982 (by filing an

amended return for 1982), or he may exclude the $10,000 performance bonus received in 1984 on his 1984 income tax return. However, C may not exclude part of the 1982 bonus and part of the 1984 bonus.

(3) *Exception for year-end payroll period.* Notwithstanding paragraph (e)(1) of this section, salary or wage payments of a cash basis taxpayer shall be attributed entirely to the year of receipt under the following circumstances:

(i) The period for which the payment is made is a normal payroll period of the employer which regularly applies to the employee;

(ii) The payroll period includes the last day of the employee's taxable year;

(iii) The payroll period does not exceed 16 days; and

(iv) The payment is part of a normal payroll of the employer that is distributed at the same time, in relation to the payroll period, that such payroll would normally be distributed, and is distributed before the end of the next succeeding payroll period.

(4) *Attribution of bonuses and substantially nonvested property to periods in which services were performed*—(i) *In general.* Bonuses and substantially nonvested property are attributable to all of the services giving rise to the income on the basis of all the facts and circumstances. If an individual receives a bonus or substantially nonvested property (as defined in § 1.83–3(b)) and it is determined to be attributable to services performed in more than one taxable year, then, for purposes of determining the amount eligible for exclusion from gross income in the year the bonus is received or the property vests, a portion of such amount shall be treated as attributable to services performed in each taxable year (or portion thereof) during the period when services giving rise to the bonus or the substantially nonvested property were performed. Such portion shall be determined by dividing the amount of the bonus or the excess of the fair market value of the vested property over the amount paid, if any, for the vested property, by the number of months in the period when services giving rise to such amount were performed, and multiplying the quotient by the number of months in such period in the taxable year. For purposes of this section, the term "month" means a calendar month. A fraction of a calendar month shall be deemed a month if it includes fifteen or more days.

(ii) *Examples.* The following examples illustrate the application of this paragraph (e)(4).

Example (1). A, an employee of M Corporation during all of 1983 and 1984, worked in the United States from January 1 through April 30, 1983, and received $12,000 of salary for that period. A worked in country F from May 1, 1983 through the end of 1984, and is a qualified individual under § 1.911–2(a) for that period. For the period from May 1 through December 31, 1983, A received $32,000 of salary. M pays a bonus on December 20, 1983 to each of M's employees in an amount equal to 10 percent of the employee's regular wages or salary for the 1983 calendar year. The amount of A's bonus is $4,400 for 1983. The portion of A's bonus that is attributable to services performed in country F and is foreign earned income for 1983 is $3,200, or $32,000×10 percent. The remaining $1,200 of A's bonus is attributable to services performed in the United States, and is not foreign earned income.

Example (2). The facts are the same as in example (1), except that M determines bonuses separately for each country based on the productivity of the employees in that country. M pays a bonus to employees in country F, in the amount of 15 percent of each employee's wages or salary earned in country F. A's country F bonus is $4,800 for 1983 ($32,000×15 percent), and is foreign earned income for 1983. If A also receives a bonus (or if A's bonus is increased) for working in the United States during 1983, that amount is not foreign earned income.

Example (3). X corporation offers its employees a bonus of $40,000 if the employee accepts employment in a foreign country and remains in a foreign country for a period of at least four years. A, an employee of X, is a calendar year and cash basis taxpayer. A accepts employment with X in foreign country F. A begins work in F on July 1, 1983 and continues to work in F for X until June 30, 1987. In 1987 X pays A a $40,000 bonus. The bonus is attributable to services A performed from July 1, 1983 through June 30, 1987. The amount of the bonus attributable to 1987 is $5,000 (($40,000÷48)×6). The amount of the bonus attributable to 1986 is $10,000 (($40,000÷48)×12). A may exclude the $10,000 attributable to 1986 only to the extent that amount could have been excluded under section 911(a)(1) had A received it in 1986. The remaining $25,000 is attributable to services performed in taxable years before 1986. Such amounts may not be excluded under section 911 because they are received after the close of the taxable year following the taxable year in which the services giving rise to the income were performed.

(iii) *Special rule for elections under section 83(b).* If an individual receives substantially nonvested property and makes an election under section 83(b) and § 1.83–2(a) to include in his gross income the amount determined under section 83(b)(1) (A) and (B) and § 1.83–2(a) for the taxable year in which the property is transferred (as defined in § 1.83–3(a)), then, for the purpose of determining the amount eligible for exclusion in the year of receipt, the individual may elect either of the following options:

(A) Substantially nonvested property may be treated as attributable entirely to services performed in the taxable year in which an election to include it in income is made. If so treated, then the amount otherwise included in gross income as determined under § 1.83–2(a) will be excludable under section 911(a) for such year subject to the limitation provided in § 1.911–3(d)(2) for such year.

(B) A portion of the substantially nonvested property may be treated as attributable to services performed or to be performed in each taxable year during which the substantial risk of forfeiture (as defined in section 83(c) and § 1.83–3(c)) exists. The portion treated as attributable to services performed or to be performed in each taxable year is determined by dividing the amount of the substantially nonvested property included in gross income as determined under § 1.83–2(a) by the number of months during the period when a substantial risk of forfeiture exists. The quotient is multiplied by the total number of months in the taxable year during which a substantial risk of forfeiture exists. The amount determined to be attributable to services performed in the year the election is made shall be excluded from gross income for such year as provided in paragraph (d)(2) of this section. Amounts treated as attributable to services performed in subsequent taxable years shall be excludable in the year of receipt only to the extent such amounts could be excluded under paragraph (d)(2) of this section in such subsequent years. An individual may obtain such additional exclusion by filing an amended return for the taxable year in which the property was transferred. The individual may only amend his or her return within the period provided by section 6511(a) and the regulations thereunder.

(5) *Moving expense reimbursements*—(i) *Source of reimbursements.* For the purpose of determining whether a moving expense reimbursement is attributable to servics performed within a foreign country or within the United States, in the absence of evidence to the contrary, the reimbursement shall be attributable to future services to be performed at the new principal place of work. Thus, a reimbursement received by an employee from his employer for the expenses of a move to a foreign country will generally be attributable to services performed in the foreign country. A reimbursement received by an employee from his employer for the expenses of a move from a foreign country to the United States will generally be attributable to services

performed in the United States. For purposes of this paragraph (e)(5), evidence to the contrary includes, but is not limited to, an agreement, between the employer and the employee, or a statement of company policy, which is reduced to writing before the move to the foreign country and which is entered into or established to induce the employee or employees to move to a foreign country. The writing must state that the employer will reimburse the employee for moving expenses incurred in returning to the United States regardless of whether the employee continues to work for the employer after the employee returns to the United States. The writing may contain conditions upon which the right to reimbursement is determined as long as the conditions set forth standards that are definitely ascertainable and the conditions can only be fulfilled prior to, or through completion of the employee's return move to the United States that is the subject of the writing. In no case will an oral agreement or statement of company policy concerning moving expenses be considered evidence to the contrary. For the purpose of determining whether a storage expense reimbursement is attributable to services performed within a foreign country, in the case of storage expenses incurred after December 31, 1983, the reimbursement shall be attributable to services performed during the period of time for which the storage expenses are incurred.

(ii) *Attribution of foreign source reimbursements to taxable years in which services are performed*—(A) *In general.* If a reimbursement for moving expenses is determined to be from foreign sources under paragraph (e)(5)(i) of this section, then for the purpose of determining the amount eligible for exclusion in accordance with paragraphs (d)(2) and (e)(2) of this section, the reimbursement shall be considered attributable to services performed in the year of the move as long as the individual is a qualified individual for a period that includes 120 days in the year of the move. The period that is used in determining the number of qualifying days for purposes of the individual's section 911(a)(1) limitation (under paragraph (d)(2) of this section) must also be used in determining whether the individual is a qualified individual for a period that includes 120 days in the year of the move. If the individual is not a qualified individual for such period, then the individual shall treat a portion of the reimbursement as attributable to services performed in the year of the move, and a portion as attributable to services performed in the succeeding taxable year, if the move is from the United States to a foreign country, or to the prior taxable year, if the move is from a foreign country to the United States. The portion of the reimbursement treated as attributable to services performed in the year of the move shall be determined by multiplying the total reimbursement by the following fraction:

$$\frac{\text{The number of qualifying days (as defined in paragraph (d)(3) of this section) in the year of the move}}{\text{The number of days in the taxable year of the move.}}$$

The remaining portion of the reimbursement shall be treated as attributable to services performed in the year succeeding or preceding the year of the move. Amounts treated as attributable to services performed in a year succeeding or preceding the year of the move shall be excludable in the year of receipt only to the extent such amounts could be excluded under paragraph (d)(2) of this section in such succeeding or preceding year.

(B) *Moves beginning before January 1, 1984.* Notwithstanding paragraph (e)(5)(ii)(A) of this section, this paragraph (e)(5)(ii)(B) shall apply for moves begun before January 1, 1984. If a reimbursement for moving expenses is determined to be from foreign sources under paragraph (e)(5)(i) of this section, then for the purpose of determining the amount eligible for exclusion in accordance with paragraphs (d)(2) and (e)(2) of this section, the reimbursement shall be considered attributable to services performed in the year of the move. However, if the individual does not qualify under section 911(d)(1) and § 1.911–2(a) for the entire taxable year of the move, then the individual shall treat a portion of the reimbursement as attributable to services performed in the succeeding taxable year, if the move is from the United States to a foreign country, or to the prior taxable year, if the move is from a foreign country to the United States. The portion of the reimbursement treated as attributable to services performed in the year succeeding or preceding the move shall be determined by multiplying the total reimbursement by the following fraction:

$$\frac{\text{The number of qualifying days (as defined in paragraph (d)(3) of this section) in the year of the move}}{\text{The number of days in the taxable year of the move.}}$$

and subtracting the product from the total reimbursement. Amounts treated as attributable to services performed in a year succeeding or preceding the year of the move shall be excludable in the year of receipt only to the extent such amounts could be excluded under paragraph (d)(2) of this section in such succeeding or preceding year.

(f) *Examples.* The following examples illustrate the application of this section.

Example (1). A is a U.S. citizen and calendar year taxpayer. A's tax home was in foreign country F and A was physically present in F for 330 days during the period from July 4, 1982 through July 3, 1983. The number of A's qualifying days in 1982 as determined under paragraph (d)(2) of this section is 181. In 1982 A receives $40,000 attributable to services performed in foreign country F in 1982. Under paragraph (d)(2) of this section A's section 911(a)(1) limitation is $37,192, that is the lesser of $40,000 (foreign earned income) or

$$\$75{,}000 \text{ (annual rate)} \times \frac{181 \text{ (qualifying days)}}{365 \text{ (days in taxable year)}}.$$

Example (2). The facts are the same as in example (1) except that in 1982 A receives $30,000 attributable to services performed in foreign country F. A excludes this amount from gross income under paragraph (d) of this section. In addition, in 1983 A receives $10,000 attributable to services performed in F in 1982 and $35,000 attributable to services performed in F in 1983. On his return for 1983, A must report $45,000 of income. A's section 911(a)(1) limitation for 1983 is the lesser of $35,000 (foreign earned income) or $49,329, the annual rate for the taxable year multiplied by a fraction the numerator of which is A's qualifying days in the taxable year and the denominator of which is the number of days in the taxable year ($80,000×184/365). On his tax return for 1983 A may exclude $35,000 attributable to services performed in 1983. A may only exclude $7,192 of the $10,000 received in 1983 attributable to services performed in 1982 because such amount is only excludable in 1983 to the extent such amount could have been excluded in 1982 subject to the section 911(a)(1) limitation for 1982 which is $37,192 ($75,000×181/365). No portion of amounts attributable to services performed in 1982 may be used in calculating A's section 911(a)(1) limitation for 1983. Thus, even though A could have excluded an additional $5,329 in 1983 if A had had more foreign earned income attributable to 1983, A may

not exclude the $2,808 of remaining foreign earned income attributable to 1982.

Example (3). C is a U.S. citizen and calendar year taxpayer. C establishes a bona fide residence and a tax home in foreign country J on March 1, 1982, and maintains a tax home and a residence in J until December 31, 1986. In March of 1982 C's employer, Y corporation, transfers stock in Y to C. The stock is subject to forfeiture if C returns to the U.S. before January 1, 1985. C elects under section 83(b) to include $15,000, the amount determined with respect to such stock under section 83(b)(1), in gross income in 1982. C's other foreign earned income in 1982 is $58,000. C elects under paragraph (e)(4)(iii)(B) of this section to treat the stock as if earned over the period of the substantial risk of forfeiture. The number of months in the period of the substantial risk of forfeiture is thirty-four. The number of months in the taxable year 1982 within the period of foreign employment is ten. For purposes of determining C's section 911(a)(1) limitation, $4,412 (($15,000/34)×10) of the amount included in gross income under section 83(b) is treated as attributable to services performed in 1982, $5,294 is treated as attributable to services to be performed in 1983, and $5,294 is treated as attributable to services to be performed in 1984. In 1982, C excludes $62,412 under section 911(a)(1). That is the lesser of foreign earned income for 1982 ($58,000+$4,412) or the annual rate for the taxable year multiplied by a fraction the numerator of which is C's qualifying days in the taxable year and the denominator of which is the number of days in the taxable year ($75,000×308/365). C continues to perform services in foreign country J throughout 1983 and 1984. C would be able to exclude the remaining $5,294 attributable to services performed in 1983 and $5,294 attributable to services performed in 1984 if those amounts would be excludable if they had been received in 1983 or 1984 respectively. If C is entitled to exclude the additional amounts, C must claim the exclusion by filing an amended return for 1982.

Example (4). D is a U.S. citizen and a calendar year taxpayer. In September, 1984 D moves to a foreign country K. D is physically present in K, and D's tax home is in K, from September 15, 1984 through December 31, 1985. D receives $6,000 in April, 1985 from his employer, as a reimbursement for expenses of moving to K, pursuant to a written agreement that such moving expenses would be reimbursed to D upon successful completion of 6 months employment in K. Under paragraph (e)(15)(i) of this section, the reimbursement is attributable to services performed in K. Under the physical presence test of § 1.911–2(a)(2)(ii), among other periods D is a qualified individual for the period of August 10, 1984 through August 9, 1985, which includes 144 days in 1984. Under paragraph (e)(5)(ii) (A) of this section, for the purpose of determining the amount eligible for exclusion, the reimbursement is considered attributable to services performed in 1984 (the year of the move) because D is a qualified individual under § 1.911–2(a) for a period that includes 120 days in 1984. The reimbursement may be excluded under paragraphs (d)(2) and (e)(2) of this section, to the extent that D's foreign earned income for 1984 that was earned and received in 1984 was less than the annual rate for the taxable year multiplied by the number of days in the taxable year over the number of days in D's taxable year ($80,000×144/366), or $31,475.

Example (5). The facts are the same as in example (4) except that D is not a qualified individual under the physical presence test, but is a qualified individual under the bona fide residence test for the period of September 15, 1984 through December 31, 1985. Under paragraph (e)(5)(ii)(A) of this section, for the purpose of determining the amount eligible for exclusion, the reimbursement is considered attributable to services performed in 1984 and 1985 because D is not a qualified individual for a period that includes 120 days in 1984 (the year of the move). The portion of the reimbursement treated as attributable to services performed in 1984 is $6,000×108/366, or $1,770, and may be excluded, subject to D's 1984 section 911(a)(1) limitation. The balance of the reimbursement, $4,230, is treated as attributable to services performed in 1985, and may be excluded to the extent provided in paragraphs (d)(2) and (e)(2) of this section.

Example (6). The facts are the same as in example (4), with the following additions. Before D moved to K, D and his employer signed a written agreement that D would perform services for the employer for at least one year, primarily in country K, and, if D did not voluntarily cease to work for the employer primarily in country K before one year had elapsed, the employer would reimburse D for one half of D's expenses, up to a maximum of $4,000, of moving back to the United States. The agreement also stated that, if D did not voluntarily leave the employment in K before two years had elapsed, the employer would reimburse D for all of D's reasonable expenses of moving back to the United States. The agreement further stated that D's right to reimbursement would not be conditioned upon the performance of services after D ceased to work in K. D worked in country K for all of 1985. On January 1, 1986, D left K and moved to the United States. In February, 1986 the employer paid D $3,500 as reimbursement for one-half of D's expenses of moving to the United States. Although D did not fulfill the condition in the agreement to receive full reimbursement, all of the conditions in the agreement set forth definitely ascertainable standards and no condition could be fulfilled after D moved back to the United States. The agreement fulfills the requirements of paragraph (e)(5)(i) of this section, and therefore is evidence that the reimbursement should not be attributable to future services to be performed at D's new principal place of work. Under the facts and circumstances, the reimbursement is attributable to services performed in K. Under paragraph (e)(5)(ii)(A) of this section, the entire reimbursement is attributable to services performed in 1985. The amount attributable to 1985 may be excluded to the extent provided in paragraphs (d)(2) and (e)(2) of this section.

§ 1.911–4 Determination of housing cost amount eligible for exclusion or deduction.

(a) *Definition of housing cost amount.* The term "housing cost amount" means an amount equal to the reasonable expenses paid or incurred (as defined in section 7701(a)(25)) during the taxable year by or on behalf of the individual attributable to housing in a foreign country for the individual and any spouse or dependents who reside with the individual (or live in a second foreign household described in paragraph (b)(5) of this section) less the base housing amount as defined in paragraph (c) of this section. The housing cost amount must be reduced by the amount of any military or section 912 allowance or similar allowance excludable from gross income that is intended to compensate the individual or the individual's spouse in whole or in part for the expenses of housing during the same period for which the individual claims a housing cost amount exclusion or deduction.

(b) *Housing expenses*—(1) *Included expenses.* For purposes of paragraph (a) of this section, housing expenses include rent, the fair rental value of housing provided in kind by the employer, utilities (other than telephone charges), real and personal property insurance, occupancy taxes not described in paragraph (b)(2)(v) of this section, nonrefundable fees paid for securing a leasehold, rental of furniture and accessories, household repairs, and residential parking.

(2) *Excluded expenses.* Housing expenses do not include:

(i) The cost of house purchase, improvements, and other costs that are capital expenditures;

(ii) The cost of purchased furniture or accessories or domestic labor (maids, gardeners, etc.);

(iii) Amortized payments of principal with respect to an evidence of indebtedness secured by a mortgage on the taxpayer's housing;

(iv) Depreciation of housing owned by the taxpayer, or amortization or depreciation of capital improvements made to housing leased by the taxpayer;

(v) Interest and taxes deductible under section 163 or 164 or other amounts deductible under section 216(a) (relating to deduction of interest and taxes by cooperative housing corporation tenant);

(vi) The expenses of more than one foreign household except as provided in paragraph (b)(5) of this section;

(vii) Expenses excluded from gross income under section 119;

(viii) Expenses claimed as deductible moving expenses under section 217; or

(ix) The cost of a pay television subscription.

(3) *Limitation.* Housing expenses are taken into account for purposes of this section only to the extent attributable to housing for portions of the taxable year within the period during which the individual satisfies the requirements of § 1.911–2(a). Housing expenses are not taken into account for the period during which the value of the individual's housing is excluded from gross income under section 119, unless the individual maintains a second foreign household described in paragraph (b)(5) of this section. If an individual maintains two foreign households, only expenses incurred with respect to the abode which bears the closest relationship, not necessarily geographic, with respect to the individual's tax home shall be taken into account, unless one of the households is a second foreign household.

(4) *Reasonableness.* An amount paid for housing shall not be treated as reasonable, for purposes of paragraph (a) of this section, to the extent that the expense is lavish or extravagant under the circumstances.

(5) *Expenses of a second foreign household*—(i) *In general.* The term "second foreign household" means a separate abode maintained by an individual outside of the U.S. for his or her spouse or dependents (who, if minors, are in the individual's legal custody or the joint custody of the individual and the individual's spouse) at a place other than the tax home of the individual because of adverse living conditions at the individual's tax home. If an individual maintains a second foreign household the expenses of the second foreign household may be included in the individual's housing expenses under paragraph (b)(1) of this section. Under no circumstances shall an individual be considered to maintain more than one second foreign household at the same time.

(ii) *Adverse living conditions.* Solely for purposes of paragraph (b)(5)(i) of this section, adverse living conditions are living conditions which are dangerous, unhealthful, or otherwise adverse. Adverse living conditions include a state of warfare or civil insurrection in the general area of the individual's tax home. Adverse living conditions exist if the individual resides on the business premises of the employer for the convenience of the employer and, because of the nature of the business (for example, a construction site or drilling rig), it is not feasible for the employer to provide housing for the individual's spouse or dependents. The criteria used by the Department of State in granting a separate maintenance allowance are relevant, but not determinative, for purposes of determining whether a separate household is provided because of adverse living conditions.

(c) *Base housing amount*—(1) *In general.* The base housing amount is equal to the product of 16 percent of the annual salary of an employee of the United States who is compensated at a rate equal to the annual salary rate paid for step 1 of grade GS–14, multiplied by the following fraction:

$$\frac{\text{The number of qualifying days}}{\text{The number of days in the taxable year}}$$

For purposes of the above fraction, the number of qualifying days is determined in accordance with § 1.911–3(d)(3).

(2) *Annual salary of step 1 of grade GS–14.* The annual salary rate for a step 1 of grade GS–14 is determined on January first of the calendar year in which the individual's taxable year begins.

(d) *Housing cost amount exclusion*—(1) *Limitation.* A qualified individual who has elected to exclude his or her housing cost amount may only exclude the lesser of the full amount of either the individual's housing cost amount attributable to employer provided amounts or the individual's foreign earned income for the taxable year. A qualified individual who elects to exclude his or her housing cost amount may not claim less than the full amount of the housing cost exclusion determined under this paragraph.

(2) *Employer provided amounts.* For purposes of this section, the term "employer provided amounts" means any amounts paid or incurred on behalf of the individual by the individual's employer which are foreign earned income included in the individual's gross income for the taxable year (without regard to section 911). Employer provided amounts include, but are not limited to, the following amounts: any salary paid by the employer to the employee; any reimbursement paid by the employer to the employee for housing expenses, educational expenses for the individual's dependents, or as part of a tax equalization plan; the fair market value of compensation provided in kind (including lodging, unless excluded under section 119, relating to meals and lodging furnished for the convenience of the employer); and any amount paid by the employer to any third party on behalf of the employee. An individual will only have earnings that are not employer provided amounts if the individual has earnings from self-employment.

(3) *Housing cost amount attributable to employer provided amounts.* For the purpose of determining what portion of the housing cost amount is excludable and what portion is deductible the following rules apply. If the individual has no income from self-employment, then the entire housing cost amount is attributable to employer provided amounts and is, therefore, excludable to the extent of the limitation provided in paragraph (d)(1) of this section. If the individual only has income from self-employment, then the entire housing cost amount is attributable to non-employer provided amounts and is, therefore, deductible to the extent of the limitation provided in paragraph (e) of this section. In all other instances, the housing cost amount attributable to employer provided amounts shall be determined by multiplying the housing cost amount by the following fraction: Employer provided amounts over foreign earned income for the taxable year. The housing cost amount attributable to non-employer provided amounts shall be determined by subtracting the portion of the housing cost amount attributable to employer provided amounts from the total housing cost amount.

(e) *Housing cost amount deduction*—(1) *In general.* If a portion of the individual's housing cost amount is determined under paragraph (d)(3) of this section to be attributable to non-employer provided amounts, the individual may deduct that amount from gross income for the taxable year but only to the extent of the individual's foreign earned income (as defined in § 1.911–3) for the taxable year in excess of foreign earned income excluded and the housing cost amount excluded from gross income for the taxable year under § 1.911–3 and this section.

(2) *Carryover.* If any portion of the individual's housing cost amount deduction is disallowed for the taxable year under paragraph (e)(1) of this section, such portion shall be carried over and treated as a deduction from gross income for the succeeding taxable year (but only for the succeeding

taxable year) to the extent of the excess, if any, of:

(i) The amount of foreign earned income for the succeeding taxable year less the foreign earned income and the housing cost amount excluded from gross income under § 1.911–3 and this section for the succeeding taxable year over,

(ii) The portion, if any, of the housing cost amount that is deductible under paragraph (e)(1) of this section for the succeeding taxable year.

(f) *Examples.* The following examples illustrate the application of this section. In all examples the annual rate for a step 1 of GS–14 as of January first of the calendar year in which the individual's taxable year begins is $39,689.

Example (1). B, a U.S. citizen is a calendar year taxpayer who was a bona fide resident of and whose tax home was located in foreign country G for the entire taxable year 1982. B receives an $80,000 salary from B's employer for services performed in G. B incurs no business expenses. B receives housing provided by B's employer with a fair rental value of $15,000. The value of the housing furnished by B's employer is not excluded from gross income under section 119. B pays $10,000 for housing expenses. B's gross income and foreign earned income for 1982 is $95,000. B elects the foreign earned income exclusion of section 911(a)(1) and the housing cost amount exclusion of section 911(a)(2). B must first compute his housing cost amount exclusion. B's housing cost amount is $18,650 determined by reducing B's housing expenses, $25,000 ($15,000 fair rental value of housing and $10,000 of other expenses), by the base housing amount of $6,350 [($39,689×.16)×365/365). Because B has no income from self-employment, the entire amount is attributable to employer provided amounts and therefore, is excludable. B's section 911(a) (1) limitation is $75,000. That is the lesser of $75,000×365/365 or $95,000−18,650. B's total exclusion for 1982 under section 911(a) (1) and (2) is $93,650.

Example(2). The facts are the same as in example (1) except that B's salary for 1982 is $70,000. B's foreign earned income for 1982 is $85,000. B's housing cost amount is $18,650, all of which is attributable to employer provided amounts. B's housing cost amount is excludable to the extent of the lesser of B's housing cost amount attributable to employer provided amounts, $18,650, or the foreign earned income for the taxable year, $85,000. Thus, B excludes $18,650 under section 911(a)(2). B's section 911(a)(1) limitation for 1982 is $66,350 (the lesser of $75,000×365/365 or $85,000−18,650). B's total exclusion for 1982 under section 911(a) (1) and (2) is $85,000.

Example (3). The facts are the same as in example (2) except that in 1983, B receives $5,000 attributable to services performed in 1982. B may exclude the entire $5,000 in 1983 because such amount would have been excludable under § 1.911–3(d)(1) had it been received in 1982.

Example (4). C is a U.S. citizen self-employed and a calendar year and cash basis taxpayer. C arrived in foreign country H on October 3, 1982, and departed from H on March 8, 1984. C's tax home was located in H throughout that period. C was physically present for 330 full days during the twelve consecutive month period August 30, 1982, through August 29, 1983. The number of C's qualifying days in 1982 is 124. During 1982 C had $35,000 of foreign earned income, none of which was attributable to employer provided amounts and $8,000 of reasonable housing expenses. C's housing cost amount is $5,843 ($8,000−[(39,689×.16)×124/365]). C elects to exclude her foreign earned income under § 1.911–3(d)(1). C's section 911(a)(1) limitation for 1982 is $25,479 (the lesser of C's foreign earned income for the taxable year ($35,000) or the annual rate for the taxable year multiplied by the number of C's qualifying days over the number of days in the taxable year ($75,000×124/365=$25,479). C may not claim the housing cost amount exclusion under section 911(a)(2) because no portion of the housing cost amount is attributable to employer provided amounts. C may deduct the lesser of her housing cost amount ($5,843) or her foreign earned income in excess of amounts excluded under section 911(a) ($35,000−25,479=$9,521). Thus, C's housing cost amount deduction is $5,843.

Example (5). The facts are the same as in example (4) except that C had $30,000 of foreign earned income for 1982, none of which was attributable to employer provided amounts. C elects to exclude $25,479 under § 1.911–3(d)(1). C may only deduct $4,521 of her housing cost amount under paragraph (e)(1) of this section because her foreign earned income in excess of amounts excluded under section 911(a) is $4,521($30,000−25,479). The $1,322 of unused housing cost amount deduction may be carried over to the subsequent taxable year.

Example (6). The facts are the same as in example (4) except that C had $15,000 of foreign earned income of 1982, none of which was attributable to employer provided amounts. C elects to exclude the entire $15,000 under § 1.911–3(d)(1). C is not entitled to a housing cost amount deduction for 1982 since she has no foreign earned income in excess of amounts excluded under section 911(a). C may carry over her entire housing cost amount deduction to 1983.

Example (7). The facts are the same as in example (6). In addition, during taxable year 1983 C had $115,000 of foreign earned income, none of which was attributable to employer provided amounts, and $40,000 of reasonable housing expenses C elects to exclude her foreign earned income under § 1.911–3(d)(1). C's section 911(a)(1) limitation is the lesser of $115,000 or $80,000 ($80,000×365/365). C's housing cost amount for 1983 is $33,650 [40,000−(39,689×.16)×365/365). Since no portion of that amount is attributable to employer provided amounts, C may not claim a housing cost amount exclusion. C may deduct the lesser of her housing cost amount ($33,650) or her foreign earned income in excess of amounts excluded under section 911(a) ($115,000−80,000=35,000). Thus, C may deduct her $33,650 housing cost amount in 1983. In addition, C may deduct $1,350 of the housing cost amount deduction carried over from taxable year 1982. ([$115.000−80,000−33,650=$1,350). The remaining $4,493 ($5,843−1,350) of the housing cost amount deduction carried over from taxable year 1982 may not be deducted in 1983 or carried over to 1984.

Example (8): D is a U.S. citizen and a calendar year and cash basis taxpayer. D is a bona fide resident of and maintains his tax home in foreign country J for all of taxable year 1984. In 1984, D earns $80,000 of foreign earned income, $60,000 of which is an employer provided amount and $20,000 of which is a non-employer provided amount. D's total housing cost amount for 1984 is $25,000. D elects to exclude, under section 911(a)(2), the portion of his housing cost amount that is attributable to employer provided amounts. D's excludable housing cost amount is $18,750; that is the total housing cost amount ($25,000) multiplied by employer provided amounts for the taxable year ($60,000) over foreign earned income for the taxable year ($80,000). D also elects to exclude his foreign earned income under § 1.911–3(d)(1). D's section 911(a)(1) limitation for 1984 is $61,250 (the lesser of $80,000−$18,750 or $80,000×366/366). D's total exclusion for 1984 under section 911(a) (1) and (2) is $80,000. D cannot claim a housing cost amount deduction in 1984 because D has no foreign earned income in excess of his foreign earned income and housing cost amount excluded from gross income for the taxable year under § 1.911–3 and this section. D may carry over his housing cost amount deduction of $6,250, the total housing cost amount less the portion attributable to employer provided amounts ($25,000−18,750), to taxable year 1985.

§ 1.911–5 Special rules for married couples.

(a) *Married couples with two qualified individuals*—(1) *In general.* In the case in which a husband and wife both are qualified individuals under § 1.911–2(a), each individual may make one or more elections under § 1.911–7 and exclude from gross income foreign earned income and exclude or deduct housing cost amounts subject to the rules of paragraph (a) (2) and (3) of this section.

(2) *Computation of excluded foreign earned income.* The amount of excludable foreign earned income is determined separately for each spouse under the rule of § 1.911–3 on the basis of the income attributable to the services of that spouse. If the spouses file separate returns each may exclude the amount of his or her foreign earned income attributable to his or her services subject to the limitations of § 1.911–3(d)(2). If the spouses file a joint return, the sum of these foreign earned income amounts so determined for each spouse may be excluded. For example, H and W both qualify under § 1.911–2(a)(2)(i) for the entire 1983 taxable year. During 1983 W earns $100,000 of foreign earned income and H earns $45,000 of

foreign earned income. H and W file a joint return for 1983. On their joint return H and W may exclude from gross income a total of $125,000. That amount is determined by adding W's section 911(a)(1) limitation, $80,000 (the lesser of $80,000×365/365 or $100,000), and H's section 911(a)(1) limitation, $45,000 (the lesser of $80,000×365/365 or $45,000).

(3) *Computation of housing cost amount*—(i) *Spouses residing together.* If the spouses reside together, and file a joint return, they may compute their housing cost amount either jointly or separately. If the spouses reside together and file separate returns, they must compute their housing cost amounts separately. If the spouses compute their housing cost amounts separately, they may allocate the housing expenses to either of them or between them for the purpose of calculating separate housing cost amounts, but each spouse claiming a housing cost amount exclusion or deduction must use his or her full base housing amount in such computation. If the spouses compute their housing cost amount jointly, then only one of the spouses may claim the housing cost amount exclusion or deduction. Either spouse may claim the housing cost amount exclusion or deduction; however, if the spouses have different periods of residence or presence and the spouse with the shorter period of residence or presence claims the exclusion or deduction, then only the expenses incurred in that shorter period may be claimed as housing expenses. The spouse claiming the exclusion or deduction may aggregate the couple's housing expenses, and subtract his or her base housing amount. For example, H and W reside together and file a joint return. H was a bona fide resident of and maintained his tax home in foreign country M from August 17, 1982 through December 31, 1983. W was a bona fide resident of and maintained her tax home in foreign country M from September 15, 1982 through December 31, 1983. During 1982, H and W earn and receive, respectively, $25,000 and $10,000 of foreign earned income. H paid $10,000 for qualified housing expenses in 1982, $7,500 of that was for qualified housing expenses incurred from September 15, 1982 through December 31, 1982. W paid $3,000 for qualified housing expenses in 1982 all of which were incurred during her period of residence. H and W may choose to compute their housing cost amount jointly. If they do so and H claims the housing cost amount exclusion his exclusion would be $10,617. H's housing expenses would be $13,000 ($10,000+$3,000) and his base housing amount would be $2,383 (($39,689×.16)×137/365=$2,383). If instead W claims the housing cost amount exclusion her exclusion would be $8,621. W's housing expenses would be $10,500 ($7,500+3,000) and her base housing amount would be $1,879 (($39,689×.16)×108/365=$1,879). If H and W file jointly and both claim a housing cost amount exclusion, then H's and W's housing cost amounts would be, respectively, $7,617 ($10,000−2,383) and $1,121 ($3,000−1,879).

(ii) *Spouses residing apart.* If the spouses reside apart, both spouses may exclude or deduct their housing cost amount if the spouses have different tax homes that are not within reasonable commuting distance (as defined in § 1.119–1(d)(4)) of each other and neither spouse's residence is within a reasonable commuting distance of the other spouse's tax home. If the spouses' tax homes, or one spouse's residence and the other spouse's tax home, are within a reasonable commuting distance of each other, only one spouse may exclude or deduct his or her housing cost amount. Regardless of whether the spouses file joint or separate returns, the amount of the housing cost amount exclusion or deduction must be determined separately for each spouse under the rules of § 1.911–4. If both spouses claim a housing cost amount exclusion or deduction directly as qualified individuals, neither may claim any such exclusion or deduction under section 911(c)(2)(B)(ii), relating to a second foreign household maintained for the other spouse. If one spouse fails to claim a housing cost amount exclusion or deduction which that spouse could claim directly, the other spouse may claim such exclusion or deduction under section 911(c)(2)(B)(ii), relating to a second foreign household maintained for the first spouse, provided that all the requirements of that section are met. Spouses may not claim more than one second foreign household and the expenses of such household may only be claimed by one spouse. For example, if both H and W are qualified individuals and H's tax home is in London and W's tax home is in Paris, then both H and W may exclude or deduct their housing cost amounts; however, H and W must compute these amounts separately regardless of whether they file joint or separate returns. If instead of living in Paris, W lives in an area where there are adverse living conditions and W maintains H's home in London, then W may add those housing expenses to her housing expenses and compute one base housing amount. In that case H may not claim a housing cost amount exclusion or deduction.

(iii) *Housing cost amount attributable to employer provided amounts.* Each spouse claiming a housing cost amount exclusion or deduction shall compute the portion of the housing cost amount that is attributable to employer provided amounts separately, based on his or her separate foreign earned income, in accordance with § 1.911–4(d)(3).

(b) *Married couples with community income.* The amount of excludable foreign earned income of a husband and wife with community income is determined separately for each spouse in accordance with paragraph (a) of this section on the basis of income attributable to that spouse's services without regard to community property laws. See sections 879 and 6013 (g) and (h) for special rules regarding treatment of community income of a nonresident alien individual married to a U.S. citizen or resident.

§ 1.911–6 Disallowance of deductions, exclusions, and credits.

(a) *In general.* No deduction or exclusion from gross income under Subtitle A of the Code or credit against the tax imposed by chapter 1 of the Code shall be allowed to the extent the deduction, exclusion, or credit is properly allocable to or chargeable against amounts excluded from gross income under section 911(a). For purposes of the preceding sentence, deductions, exclusions, and credits which are definitely related (as provided in § 1.861–8), in whole or in part, to earned income shall be allocated and apportioned to foreign earned income and U.S. source earned income in accordance with the rules contained in § 1.861–8. Deductions, exclusions, and credits which are definitely related to all gross income under § 1.861–8, including deductions for interest described in § 1.861–8(e)(2)(ii), are definitely related, in whole or in part, to earned income. In the case of interest expense allocable, in whole or in part, to foreign earned income under § 1.861–8(e)(2)(ii), the expense shall normally be apportioned under option one of the optional gross income methods of apportionment (§ 1.861–8(e)(2)(v)i(A)), but without regard to conditions (*1*) and (*2*) of subdivision (vi)(A) (the fifty percent conditions). Such interest expense shall not normally be apportioned under the asset method of § 1.861–8(e)(2)(v). This is because, where section 911 is the operative section, the expense normally relates more closely to gross income generated from activities than to the amount of capital utilized or invested in activities or property. Deductions that are allocated and apportioned to foreign

earned income must then be allocated and apportioned to foreign earned income that is excluded under section 911(a). If an individual has foreign earned income from both self-employment and other employment, the amount excluded under section 911(a)(1) shall be deemed to include a pro rata amount of the self-employment income and the income from other employment; thus, a pro rata portion of deductible expenses attributable to self-employment income must be disallowed. For purposes of section 911 (d)(6) and this section only, deductions, exclusions, or credits which are not definitely related to any class of gross income shall not be allocable or chargeable to excluded amounts and are, therefore, deductible to the extent allowed by chapter 1 of the Code. Examples of deductions that are not definitely related to a class of gross income are personal and family medical expenses, qualified retirement contributions (but see section 219(b)(1)), real estate taxes and mortgage interest on a personal residence, charitable contributions, alimony payments, and deductions for personal exemptions. In addition, for purposes of this section, amounts excludable or deductible under section 911 or 119 shall not be allocable or chargeable to other amounts excluded under section 911(a). Thus, an individual's housing cost amount which is excludable or deductible under § 1.911–4(d) for a taxable year is not apportioned in part to the individual's foreign earned income which is excluded for such year under § 1.911–3(d). Therefore, the entire amount of such exclusion or deduction is allowed to the extent provided in § 1.911–4. This section does not affect the time for claiming any deduction, exclusion, or credit that is not allocated or apportioned to excluded amounts.

(b) *Moving expenses*—(1) *In general.* No deduction shall be allowed for moving expenses under section 217 to the extent the deduction is properly allocable to or chargeable against amounts of foreign earned income excluded from gross income under section 911(a). If an individual's new principal place of work is in a foreign country, deductible moving expenses will be allocable to foreign earned income. If an individual treats a reimbursement from his employer for the expenses of a move from a foreign country to the United States as attributable to services performed in a foreign country under § 1.911–3(e)(5)(i), then deductible moving expenses attributable to that move will be allocable to foreign earned income. If the individual is a qualified individual who elects to exclude foreign earned income under section 911(a), then some or all of such moving expenses must be disallowed as a deduction.

(2) *Attribution of moving expense deduction to taxable years in which services are performed.* If a moving expense deduction is properly allocable to foreign earned income, the deduction shall be considered attributable to services performed in the year of the move as long as the individual is a qualified individual under § 1.911–2(a) for a period that includes 120 days in the year of the move. If the individual is not a qualified individual for such period, then the individual shall treat the deduction as attributable to services performed in both the year of the move and the succeeding taxable year, if the move is from the United States to the foreign country, or the prior taxable year, if the move is from a foreign country to the United States. Notwithstanding the preceding two sentences, storage expenses incurred after December 31, 1983 shall be treated as attributable to services performed in the year in which the expenses are incurred.

(3) *Formula for disallowance of moving expense deduction.* The portion of the moving expense deduction that is disallowed shall be determined by multiplying the moving expense deduction by a fraction the numerator of which is all amounts excluded under section 911(a) for the year or years to which the deduction is attributable (under paragraph (b)(2) of this section) and the denominator of which is foreign earned income (as defined in § 1.911–3(a)) for that year or years.

(4) *Effect of disallowance based on attribution of deduction to subsequent year's income.* An individual may claim a moving expense deduction in the taxable year in which the amount of the expense is paid or incurred even if attributable, in part, to the succeeding year. However, at such time as the individual excludes income under section 911(a) for the year or years to which the deduction is attributable, the individual shall either—

(i) File an amended return for the year in which the deduction was claimed that does not claim the portion of the deduction that is disallowed because it is chargeable against excluded income, or

(ii) Include in income for the year following the year in which the deduction was claimed an amount equal to the amount of the deduction that is disallowed.

Any amount included in income under paragraph (b)(4)(ii) of this section is not foreign earned income.

(5) *Moves beginning before January 1, 1984.* Notwithstanding paragraph (b) (1) through (3) of this section, the rules of this paragraph (b)(5) shall apply for moves beginning before January 1, 1984.

(i) *Individual qualifies for the entire taxable year of the move.* If the individual is a qualified individual for the entire taxable year of the move, then the amount of moving expense disallowed shall be determined by multiplying the moving expense deduction otherwise allowable by a fraction the numerator of which is the foreign earned income excluded under section 911(a) for the taxable year of the move and the denominator of which is the foreign earned income for the same taxable year.

(ii) *Individual qualifies for less than the entire taxable year of the move.* If the individual is a qualified individual for less than the entire taxable year of the move, then, for the purpose of determining the portion of the otherwise allowable moving expense deduction that is disallowed, the individual must attribute a portion of the otherwise allowable moving expense deduction either to the succeeding taxable year, if the move is from the United States to a foreign country, or to the prior taxable year, if the move is from a foreign country to the United States. The portion of the moving expense deduction treated as attributable to services performed in the year of the move shall be determined by multiplying the otherwise allowable moving expense deduction by the following fraction:

$$\frac{\text{The number of qualifying days (as defined in § 1.911–3(d)(3) in the year of the move}}{\text{The number of days in the taxable year of the move.}}$$

The portion of the moving expense deduction treated as attributable to the year succeeding or preceding the move shall be determined by subtracting the portion of the moving expense deduction that is attributable to the year of the move from the total moving expense deduction. The allocation of a portion of the moving expense deduction to a succeeding or preceding taxable year does not affect the time for claiming the allowable moving expense deduction. The portion of the moving expense deduction that is disallowed shall be determined by multiplying the moving expense deduction attributable to the year of the move or the succeeding or preceding year, as the case may be, by a

fraction the numerator of which is amounts excluded under section 911(a) for that year and the denominator of which is foreign earned income for that year.

(c) *Foreign taxes*—(1) *Amount disallowed.* No deduction or credit is allowed for foreign income, war profits, or excess profits taxes paid or accrued with respect to amounts excluded from gross income under section 911. To determine the amount of disallowed foreign taxes, multiply the foreign tax imposed on foreign earned income (as defined in § 1.911–3(a)) received or accrued during the taxable year by a fraction, the numerator of which is amounts excluded under section 911(a) in such taxable year less deductible expenses properly allocated to such amounts (see paragraphs (a) and (b) of this section), and the denominator of which is foreign earned income (as defined in § 1.911–3(a)) received or accrued during the taxable year less deductible expenses properly allocated or apportioned thereto. For the purpose of determining the extent to which foreign taxes are disallowed, the housing cost amount deduction is treated as definitely related to foreign earned income that is not excluded. If the foreign tax is imposed on foreign earned income and some other income (for example earned income from sources within the United States or an amount not subject to tax in the United States), and the taxes on the other amount cannot be segregated, then the denominator equals the total of the amounts subject to tax less deductible expenses allocable to all such amounts.

(2) *Definitions and special rules*—(i) *Taxable year.* For purposes of paragraph (c)(1) of this section, the term "taxable year" means the individual's taxable year for U.S. tax purposes. Such term includes the portion of any foreign taxable year within the individual's U.S. taxable year and excludes the portion of any foreign taxable year not within the individual's U.S. taxable year.

(ii) *Apportionment of foreign taxes.* For purposes of this paragraph (c), foreign taxes imposed on foreign earned income shall be deemed to accrue, on a pro rata basis, to income as the income is received or accrued. The taxes so accrued shall be apportioned to the taxable year during which the income is received or accrued. This rule applies for all individuals, regardless of their method of accounting.

(iii) *Effect of disallowance.* The disallowance of foreign taxes under this paragraph (c) shall not affect the time for claiming any deduction or credit for foreign taxes paid. Rather, the disallowance shall only affect the amount of taxes considered paid or accrued to any foreign country.

(iv) *Interest on foreign taxes.* Any interest expense incurred on a liability for foreign taxes is allocated and apportioned not under this paragraph (c) but under paragraph (a) of this section to foreign earned income and then to excluded foreign earned income and to that extent disallowed as a deduction under paragraph (a). In that regard, see also § 1.861–8(e)(2) for the specific rules for allocation and apportionment of interest expense.

(d) *Examples.* The following examples illustrate the application of this section.

Example (1). In 1982 A, an architect, operates his business as a sole proprietorship in which capital is not a material income producing factor. A receives $1,000,000 in gross receipts, all of which is foreign source earned income, and incurs $500,000 of otherwise deductible business expenses definitely related to the foreign earned income. A elects to exclude $75,000 under section 911(a)(1). The expenses must be apportioned to excluded earned income as follows: $500,000×$75,000/1,000,000. Thus, $37,500 of the business expenses are not deductible.

Example (2). The facts are the same as in example (1), except that $100,000 of A's gross receipts is U.S. source earned income and $68,000 of A's business expenses are attributable to the U.S. source earned income. Thus, A has $900,000 of foreign earned income and $432,000 of deductions allocated to foreign earned income. The expenses apportioned to excluded earned income are $432,000×$75,000/$900,000, or $36,000, which are not deductible.

Example (3). B is a U.S. citizen, calendar year and cash basis taxpayer. B moves to foreign country N and maintains a tax home and is physically present there from July 1, 1984 through May 28, 1985. Among other possible periods, B is a qualified individual for 219 days in the year of the move. B pays $6,000 of otherwise deductible moving expenses in 1984. For 1984, B's foreign earned income is $60,000 and B excludes $47,869 ($80,000×219/366) under section 911(a). Under paragraph (b)(2) of this section, B's moving expenses are attributable to services performed in 1984. Under paragraph (b)(3) of this section, $6,000×$47,869/$60,000, or $4,789, of B's moving expense deduction is disallowed. B may deduct $1,211 of moving expenses on his 1984 return.

Example (4). The facts are the same as in example (3) except that B maintains a tax home and is physically present in foreign country N from October 9, 1984 through September 3, 1985. Among other possible periods, B is a qualified individual for no more than 119 days in 1984 and 281 days in 1985. B's foreign earned income for 1984 is $60,000. B's foreign earned income for 1985 is $150,000. Because B is a qualified individual for less than 120 days in the year of the move, under paragraph (b)(2) of this section, B's moving expenses are attributable to services performed in 1984 and 1985. At the close of 1984, B may either seek an extension of time to file under § 1.911–7(c) or may file an income tax return without claiming the exclusions or deduction under section 911. B does not seek an extension and files without excluding foreign earned income; thus B may deduct his moving expenses in full. B later amends his 1984 return and excludes foreign earned income for that year. B excludes foreign earned income for 1985. B must determine the portion of the moving expense deduction that is disallowed. The portion of the moving expense deduction that is disallowed is determined by multiplying the otherwise allowable moving expense deduction by a fraction. The numerator of the fraction is the sum of amounts excluded under section 911(a) for 1984 and 1985, that is $26,082 or $80,000×119/365, plus $61,589, or $80,000×281/365, which totals $87,671. The denominator of the fraction is the sum of foreign earned income for 1984 and 1985, that is $60,000 plus $150,000, or $210,000. B's allowable moving expense deduction is $3,495, or $6,000−($6,000×$87,671/$210,000). If B does not file an amended 1984 return (and does not exclude foreign earned income for 1984), but excludes foreign earned income under section 911(a) for 1985, a portion of his moving expense deduction is disallowed, based on the same formula. The amount disallowed is $6,000×$61,589/$210,000, or $1,760. This amount may be recaptured either by filing an amended return for 1984 or by including it in income for 1985 (in which case it is not foreign earned income).

Example (5). C is a U.S. citizen, a self-employed individual, and a cash basis and calendar year taxpayer. For the entire 1982 taxable year C maintained his tax home and his bona fide residence in foreign country P. During 1982 C earned and received $120,000 of foreign earned income, none of which was attributable to employer provided amounts. C paid $40,000 of business expenses. C elected to exclude foreign earned income under section 911(a)(1) and claimed a housing cost amount deduction of $15,000. C received $10,000 of foreign source interest income which was included with C's earned income in a single tax base and taxed at graduated rates. For 1982, C paid $30,000 in income tax to foreign country P. The amount of C's business expenses that is properly apportioned to excluded amounts (and therefore, not deductible) equals $25,000, which is determined by multiplying the otherwise allowable deductions by C's excluded amounts over C's foreign earned income ($40,000×75,000/120,000). The amount of country P tax that is properly apportioned to excluded amounts (and therefore, not deductible or creditable) equals $20,000, which is determined by multiplying the tax of $30,000 by the following fraction:

$$\frac{\text{\$50,000 (\$75,000 excluded amounts less \$25,000 of deductible expenses allocable thereto)}}{\text{\$75,000 (([\$120,000 foreign earned income less \$40,000 of deductible expenses allocable thereto) less \$15,000 housing cost amount deduction allocable thereto) plus \$10,000 other taxable income).}}$$

Example (6). D is a U.S. citizen and an accrual basis and calendar year taxpayer for U.S. tax purposes. For the entire period from January 1, 1982 through December 31, 1983, D maintains his tax home and his bona fide residence in foreign country R. For purposes of R's income tax, D is a cash basis taxpayer and uses a fiscal year that begins on April 1 and ends on the following March 31. During his entire period of residence in R, D receives foreign earned income of $10,000 each month, all of which is attributable to employer provided amounts. For his foreign taxable year ending March 31, 1982, D pays $10,000 of income tax to R. For his foreign taxable year ending March 31, 1983, D pays $54,000 of income tax to R. Under paragraph (c)(2)(ii) of this section, all of the $10,000 of tax paid for this foreign taxable year ending March 31, 1982 is imposed on foreign earned income received in 1982, as is $40,500, or $^9/_{12}\times\$54{,}000$, of tax paid for his foreign taxable year ending March 31, 1983. (D received $10,000 per month for the last 3 months of his foreign taxable year ending March 31, 1982, all of which are within his U.S. taxable year ending December 31, 1982 under paragraph (c)(2)(i) of this section, and $10,000 per month for each month of his foreign taxable year ending March 31, 1983, of which the first 9 months are within his U.S. taxable year ending December 31, 1982. Under paragraph (c)(2)(ii) of this section, foreign taxes are deemed to accrue on a pro rata basis to income as it is received or accrued. Thus, all of the $10,000 of foreign taxes imposed on the income received during D's foreign taxable year ending March 31, 1982 accrue to D's 1982 foreign earned income, as do $^9/_{12}$ (or $90,000/120,000) of foreign taxes imposed on income received during D's foreign taxable year ending March 31, 1983, for purposes of determining the amount of D's foreign taxes that is disallowed.) For 1982, D has no deductible expenses, and elects to exclude his housing cost amount of $21,000 under section 911(a)(2) and foreign earned income of $75,000 under section 911(a)(1). The amount of D's foreign taxes disallowed for deduction or credit purposes for 1982 is $8,000 (that is, $10,000\times\$96{,}000/\$120{,}000$) of the taxes for his foreign taxable year ending March 31, 1982, plus $32,400 (that is, $40,500\times\$96{,}000/\$120{,}000$) of the taxes for his foreign taxable year ending March 31, 1983, or $40,400. From 1982, D has $2,000 ($10,000−$8,000) of deductible or creditable taxes accrued on March 31, 1982, and $8,100 ($40,500−$32,400) of deductible or creditable taxes accrued on March 31, 1983, after the disallowance based on his 1982 excluded income.

Example (7). E is a United States citizen, calendar year and cash basis taxpayer. E is physically present in and establishes his tax home in foreign country S on May 1, 1981. For purposes of country S, E's taxable year begins on April 1 and ends the following March 31. E receives foreign earned income of $15,000 each month beginning on May 1, 1981. At the end of his foreign taxable year ending on March 31, 1982, E pays $70,000 of income tax to S on $165,000 of foreign earned income. Under section 911, as in effect for taxable years beginning before January 1, 1982, E may not exclude any income that is earned or received during 1981. None of E's taxes paid in 1982 that are attributable to income earned or received in 1981 are subject to disallowance because, under paragraph (c)(2)(ii) of this section, the only taxes disallowed are those deemed to accrue on income earned and received after December 31, 1981, and excluded from gross income. The amount of E's taxes paid in 1982 that are attributable to 1981 is $50,909, or $70,000\times\$120{,}000/\$165{,}000$. E elects to exclude foreign earned income for 1982. The amount of E's taxes paid to S in 1982 that accrue to 1982 foreign earned income, and are therefore subject to disallowance based on excluded income, is $19,091, or $70,000\times\$45{,}000/\$165{,}000$.

§ 1.911–7 Procedural rules.

(a) *Elections of a qualified individual*—(1) *In general.* In order to receive either exclusion provided by section 911(a), a qualified individual must elect, separately with respect to each exclusion, to exclude foreign earned income under section 911(a)(1) and the housing cost amount under section 911(a)(2). Any such elections may be made on Form 2555 or on a comparable form. Each election must be filed either with the income tax return, or with an amended return, for the first taxable year of the individual for which the election is to be effective. An election once made remains in effect for that year and all subsequent years unless revoked under paragraph (b) of this section. Each election shall contain information sufficient to determine whether the individual is a qualified individual as provided in § 1.911–2. The statement shall include the following information:

(i) The individual's name, address, and social security number;

(ii) The name of the individual's employer;

(iii) Whether the individual claimed exclusions under section 911 for earlier years after 1981 and within the five preceding taxable years;

(iv) Whether the individual has revoked a previously made election and the taxable year for which such revocation was effective;

(v) The exclusion or exclusions the individual is electing;

(vi) The foreign country or countries in which the individual's tax home is located and the date when such tax home was established;

(vii) The status (either bona fide residence or physical presence) under which the individual claims the exclusion;

(viii) The individual's qualifying period of residence or presence;

(ix) The individual's foreign earned income for the taxable year including the fair market value of all noncash remuneration; and,

(x) If the individual elects to exclude the housing cost amount, the individual's housing expenses.

(2) *Requirement of a return*—(i) *In general.* In order to make a valid election under this paragraph (a), the election must be made:

(A) With an income tax return that is timely filed (including any extensions of time to file),

(B) With a later return filed within the period prescribed in section 6511(a) amending the foregoing timely filed income tax return, or

(C) With an original income tax return that is filed within one year after the due date of the return (determined without regard to any extension of time to file); this one year period does not constitute an extension of time for any purpose—it is merely a period during which a valid election may be made on a late return.

(ii) *Election for 1982 and 1983 taxable years.* Solely for purposes of paragraph (a)(2)(i)(A) of this section, an income tax return for any taxable year beginning before January 1, 1984 shall be considered timely filed if it is filed on or before July 23, 1985.

(3) *Housing cost amount deduction.* An individual does not have to make an election in order to claim the housing cost amount deduction. However, such individual must provide the Commissioner with information sufficient to determine the individual's correct amount of tax. Such information shall include the following: The individual's name, address, and social security number; the name of the individual's employer; the foreign country in which the individual's tax home was established; the status under which the individual claims the deduction; the individual's qualifying period of residence or presence; the individual's foreign earned income for the taxable year; and the individual's housing expenses.

(4) *Effect of immaterial error or omission.* An inadvertent error or omission of information required to be provided to make an election under this paragraph (a) shall not render the election invalid if the error or omission is not material in determining whether the individual is a qualified individual or whether the individual intends to make the election.

(b) *Revocation of election*—(1)—*In general.* An individual may revoke any election made under paragraph (a) of this section for any taxable year. A revocation must be made separately with respect to each election. The individual may revoke an election for any taxable year, including the first

taxable year for which an election was effective, by filing a statement that the individual is revoking one or more of the previously made elections. The statement must be filed with the income tax return, or with an amended return, for the first taxable year of the individual for which the revocation is to be effective. A revocation once made is effective for that year and all subsequent years. If an election is revoked for any taxable year, including the first taxable year for which the election was effective, the individual may not, without the consent of the Commissioner, again make the same election until the sixth taxable year following the taxable year for which the revocation was first effective. For example, a qualified individual makes an election to exclude foreign earned income under section 911(a)(1) and files it with his 1982 income tax return. The individual files 1983 and 1984 income tax returns on which he excludes his foreign earned income. Then, within 3 years after filing his 1982 income tax return, the individual files an amended 1982 income tax return with a statement revoking his election to exclude foreign earned income under section 911(a)(1). The revocation of the election is effective for taxable years 1982, 1983, and 1984. The individual may not elect to exclude income under section 911(a)(1) for any taxable year before 1988, unless he obtains consent to reelect under paragraph (b)(2) of this section.

(2) *Reelection before sixth taxable year after revocation.* If an individual revoked an election under paragraph (b)(1) of this section and within five taxable years the individual wishes to reelect the same exclusion, then the individual may apply for consent to the reelection. The application for consent shall be made by requesting a ruling from the Associate Chief Counsel (Technical), National Office, Internal Revenue Service, 1111 Constitution Avenue NW., Washington, D.C. 20224. In determining whether to consent to reelection the Associate Chief Counsel or his delegate shall consider any facts and circumstances that may be relevant to the determination. Relevant facts and circumstances may include the following: a period of United States residence, a move from one foreign country to another foreign country with differing tax rates, a substantial change in the tax laws of the foreign country of residence or physical presence, and a change of employer.

(c) *Returns and extensions*—(1) *In general.* Any return filed before completion of the period necessary to qualify an individual for any exclusion of deduction provided by section 911 shall be filed without regard to any exclusion or deduction provided by that section. A claim for a credit or refund of any overpayment of tax may be filed, however, if the taxpayer subsequently qualifies for any exclusion or deduction under section 911. See section 6012(c) and § 1.6012–1(a)(3), relating to returns to be filed and information to be furnished by individuals who qualify for any exclusion or deduction under section 911.

(2) *Extensions.* An individual desiring an extension of time (in addition to the automatic extension of time granted by § 1.6081–2) for filing a return until after the completion of the qualifying period described in paragraph (c)(1) of this section for claiming any exclusion or deduction under section 911 may apply for an extension. An individual whose moving expense deduction is attributable to services performed in two years may apply for an extension of time for filing a return until after the end of the second year. The individual may make such application on Form 2350 or a comparable form. The application must be filed with the Director, Internal Revenue Service Center, Philadelphia, Pennsylvania 19255. The application must set forth the facts relied on to justify the extension of time requested and must include a statement as to the earliest date the individual expects to become entitled to any exclusion or deduction by reason of completion of the qualifying period.

(d) *Declaration of estimated tax.* In estimating gross income for the purpose of determining whether a declaration of estimated tax must be made for any taxable year, an individual is not required to take into account income which the individual reasonably believes will be excluded from gross income under the provisions of section 911. In computing estimated tax, however, the individual must take into account, among other things, the denial of the foreign tax credit for foreign taxes allocable to the excluded income (see § 1.911–6(c)).

§ 1.911–8 Former deduction for certain expenses of living abroad.

For rules relating to the deduction for certain expenses of living abroad applicable to taxable years beginning before January 1, 1982, see 26 CFR 1.913–1 through 1.913–13 as they appeared in the Code of Federal Regulations revised as of April 1, 1982.

§ 1.913–1—1.913–13 [Removed]

Par. 3. Sections 1.913–1 through 1.913–13 are removed.

Employment Tax Regulations

Par. 4. Section 31.3401(a)(8)(A)–1 is amended by revising paragraph (a)(1)(ii), (2)(i) and (3), and adding paragraph (a)(4). The revised and added paragraphs read as follows:

§ 31.3401(a)(8)(A)–1 Remuneration for services performed outside the United States by citizens of the United States.

(a) * * *

(1) * * *

(ii) Remuneration paid by an employer to an employee constitutes wages, and hence is subject to withholding only to the extent that the remuneration is expected to exceed the aggregate amount which is excludable from the employee's gross income under section 911(a). For amounts paid after December 31, 1984, the determination of the amount subject to withholding shall be made by applying the excludable amount, on a pro rata basis, to each payment of remuneration to the employee. For this purpose, an employer is not required to ascertain information with respect to amounts received by his employee from any other source; but, if the employer has such information, he shall take it into account in determining whether the earned income of the employee is in excess of the applicable limitation. For purposes of section 911(d)(5) and § 1.911–2(c), relating to an employee who states to the authorities of a foreign country that he is not a resident of that country, the employer is not required to ascertain whether such a statement has been made; but if an employer knows that such a statement has been made, he shall presume that the employee is not a bona fide resident of that country, unless the employer also knows that the authorities of the foreign country have determined, notwithstanding the statement, that the employee is a resident of that country. For purposes of section 911(d)(1) or § 1.911–2(a) relating to the definition of a qualified individual, the reasonable belief contemplated by the statute may be based on a presumption as set forth in subparagraph (2) or (3) of this paragraph. For purposes of sections 911(a)(2) and 911(c)(2) and § 1.911–4(b) and (d)(1), relating to the housing cost amount exclusion and the definition of housing expenses, the reasonable belief contemplated by the statute may be based on the presumption set forth in subparagraph (4) of this paragraph.

(2)(i) The employer may, in the absence of cause for a reasonable belief to the contrary, presume that an employee will maintain a tax home in a foreign country or countries and be a

bona fide resident of a foreign country or countries, within the meaning of section 911(d)(1), for an uninterrupted period which includes each taxable year of the employee, or applicable portion thereof, in respect of which the employee properly executes and delivers to the employer a statement that the employee meets or will meet the requirement of § 1.911–2(a) relating to maintaining a tax home and a bona fide residence in a foreign country for the taxable year. This statement must set forth the facts alleged as the basis for this determination and contain a declaration by the employee that the statement is made under the penalties of perjury. Sample forms of acceptable statements may be obtained by writing to the Foreign Operations District, Internal Revenue Service, Washington, D.C. 20225 (Form IO–673).

(ii) * * *

(3) The employer may, in the absence of cause for a reasonable belief to the contrary, presume that an employee will maintain a tax home in a foreign country or countries and be present in a foreign country or countries during at least 330 full days during any period of twelve consecutive months, within the meaning of section 911(d)(1), and that such period includes each taxable year of the employee, or applicable portion thereof, in respect of which the employee properly executes and delivers to the employer a statement that the employee meets or will meet the requirements of § 1.911–2(a) relating to maintaining a tax home and being physically present in a foreign country for the taxable year. This statement must set forth the facts alleged as the basis for this determination and contain a declaration by the employee that the statement is made under the penalties of perjury. Sample forms of acceptable statements may be obtained by writing to the Foreign Operations District, Internal Revenue Service, Washington, D.C. 20225 (Form IO–673).

(4) The employer may, in the absence of cause for a reasonable belief to the contrary, presume that an employee's housing cost amount will be the amount shown on a statement properly executed and delivered to the employer. This statement must set forth the employee's estimation of the following items: housing expenses (as defined in § 1.911–4(b)), the housing cost amount exclusion (as defined in § 1.911–4(d)(1)), and the qualifying period (as defined in § 1.911–2(a)). The statement must contain a declaration by the employee that it is made under the penalties of perjury. Sample forms of acceptable statements may be obtained by writing to the Foreign Operations District, Internal Revenue Service, Washington, D.C. 20225 (IO–673). The employer may not rely on a statement from an employee if the employer, based on his or her knowledge of housing costs in the vicinity of the employee's tax home (as defined in § 1.911–2(b)), believes the employee's housing expenses are lavish or extravagant under the circumstances.

(Approved by the Office of Management and Budget under control numer 1545–0067)

This Treasury decision is issued under the authority contained in section 911 (95 Stat. 194; 26 U.S.C. 911) and section 7805 (68A Stat. 917; U.S.C. 7805) of the Internal Revenue Code of 1954.

Approved by the Office of Management and Budget under control number 1545–0067.

Roscoe L. Egger, Jr.,

Commissioner of Internal Revenue.

Approved: December 21, 1984.

Ronald A. Pearlman,

Acting Assistant Secretary of the Treasury.

[FR Doc. 85–1625 Filed 1–17–85; 1:10 pm]

BILLING CODE 4830–01–M

Bureau of Alcohol, Tobacco and Firearms

27 CFR Part 9

[T.D. ATF–196; Re: Notice No. 541]

Sonoma Mountain Viticultural Area; Establishment

AGENCY: Bureau of Alcohol, Tobacco and Firearms (ATF), Department of the Treasury.

ACTION: Final rule, Treasury decision.

SUMMARY: This final rule establishes a viticultural area in Sonoma County, California, known as "Sonoma Mountain." The establishment of viticultural areas and the subsequent use of viticultural area names as appellations of origin in wine labeling and advertising will help consumers better identify wines they purchase. The use of this viticultural area as an appellation of origin will also help winemakers distinguish their products from wines made in other areas.

EFFECTIVE DATE: February 22, 1985.

FOR FURTHER INFORMATION CONTACT: John A. Linthicum, FAA, Wine and Beer Branch, (202) 566–7626.

SUPPLEMENTARY INFORMATION:

Background

On August 23, 1978, ATF published Treasury Decision ATF–53 (43 FR 37672, 54624) revising regulations in 27 CFR Part 4. These regulations allow the establishment of definitive viticultural areas. The regulations also allow the name of an approved viticultural area to be used as an appellation of origin on wine labels and in wine advertisements.

On October 2, 1979, ATF published Treasury Decision ATF–60 (44 FR 56692) which added a new Part 9 to 27 CFR, providing for the listing of approved American viticultural areas, the names of which may be used as appellations of origin.

Section 4.25a(e)(1), Title 27, CFR, defines an American viticultural area as a delimited grape-growing region distinguishable by geographical features. Section 4.25a(e)(2) outlines the procedure for proposing an American viticultural area. Any interested person may petition ATF to establish a grape-growing region as a viticultural area.

Mr. David Steiner, a grape grower in the area, petitioned ATF for the establishment of a viticultural area in Sonoma County, California, to be known as "Sonoma Mountain." In response to this petition, ATF published a notice of proposed rulemaking (Notice No. 541) in the **Federal Register** on September 5, 1984 (49 FR 35027) proposing the establishment of the Sonoma Mountain viticultural area.

General Description

The Sonoma Mountain viticultural area is entirely included within the approved Sonoma Valley and North Coast viticultural areas. The proposed Sonoma Mountain area consists of approximately 5,000 acres containing 633 acres of grapevines.

Name

Sonoma Mountain is a prominent geographical feature which has been historically known by this name. The name "Sonoma" was first given to the area by General Mariano Guadalupe Vallejo, believing that it was the Indian word for Valley of the Moon, a name applied to Sonoma Valley by the Indians. General Vallejo established the town of Sonoma in 1835. The name "Sonoma," which applies to the valley, was also applied to the range on the western side of the valley, and to the most prominent peak of that range.

Geographical Features Which Affect Viticultural Features

The Sonoma Mountain area is distinguished from surrounding areas by a "thermal belt" phenomenon common on the slopes of valleys in Mediterranean climate systems. The thermal belt phenomenon, characterized by drainage of cold air and fog from the slopes to lower elevations, is manifested

by lower maximum temperatures and higher minimum temperatures, year-round, than lower elevations. In the Sonoma Valley, the lowest elevation of the thermal belt is generally considered to be around 400 feet above mean sea level. At a certain high elevation, the thermal belt phenomenon would be expected to dissipate, due to the overall lowering of temperatures common at higher elevations. The upper point at which the thermal belt climate phenomenon is overshadowed by the effect of higher elevation has not been accurately determined on Sonoma Mountain because the steep terrain of the higher elevations makes most agricultural activities impractical.

Location	Elevation (feet)	Mean high temperature (°F)	Mean low temperature (°F)
Steiner Vineyard	1,000	74.71	52.43
Laurel Glen	800	80.25	52.96
Sobre Vista	600	74.50	52.99
Averages		76.49	52.80
Valley Floor Temperatures			
Matanzas Creek Vnyd	500	77.60	49.10
Grand Cru Vineyards	250	80.82	48.71
Hill Rd. weather sta.	200	80.46	47.74
Averages		79.63	48.52

The petitioner claims that Laurel Glen is more remote from marine influences and this accounts for the higher mean high temperature. However, the mean low temperature is consistent with other mountain temperatures, in contrast to valley floor temperatures.

Boundaries

The eastern boundary of the approved area is the 400-foot contour line, the lower elevation of the thermal belt phenomenon, as previously discussed. The western boundary is the steep terrain beginning at elevations of about 1200 to 1600 feet above mean sea level. The steep terrain is a geographical feature which makes viticulture impractical. Moreover, the thermal belt phenomenon is dissipated at higher altitudes. Therefore, the western boundary uses contour lines at elevations above which viticultural activities are impractical, and above which the thermal belt phenomenon is dissipated.

The boundary of the Sonoma Mountain viticultural area proposed in Notice No. 541 (proposed § 9.102) is adopted unchanged.

No Comments Received

ATF received no comments in response to Notice No. 541. Therefore, the proposed viticultural area is adopted as proposed.

Miscellaneous

ATF does not wish to give the impression by approving Sonoma Mountain as a viticultural area that it is endorsing the quality of the wine from this area. ATF is approving this area as being distinct and not better than other areas. By approving this area, Sonoma Mountain wine producers would be allowed to claim a distinction on labels and in advertisements as to the origin of the grapes. Any commercial advantage gained can only come from consumer acceptance of Sonoma Mountain wines.

Regulatory Flexibility Act

The provisions of the Regulatory Flexibility Act relating to a final regulatory flexibility analysis (5 U.S.C. 604) are not applicable to this final rule because it will not have a significant economic impact on a substantial number of small entities. The final rule will not impose, or otherwise cause, a significant increase in reporting, recordkeeping, or other compliance burdens on a substantial number of small entities. The final rule is not expected to have significant secondary or incidental effects on a substantial number of small entities.

Accordingly, it is hereby certified under the provisions of section 3 of the Regulatory Flexibility Act (5 U.S.C. 605(b)) that this final rule, will not have a significant economic impact on a substantial number of small entities.

Executive Order 12291

In compliance with Executive Order 12291, ATF has determined that this final rule is not a "major rule" since it will not result in:

(a) An annual effect on the economy of $100 million or more;

(b) A major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or

(c) Significant adverse effects on competition, employment, investment, productivity, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets.

Paperwork Reduction Act

The provisions of the Paperwork Reduction Act of 1980, Pub. L. 96-511, 44 U.S.C. Chapter 35, and its implementing regulations, 5 CFR Part 1320, do not apply to this final rule because no requirement to collect information is imposed.

List of Subjects in 27 CFR Part 9

Administrative practice and procedure, Consumer protection, Viticultural areas, Wine.

Drafting Information

The principal author of this document is John A. Linthicum, FAA, Wine and Beer Branch, Bureau of Alcohol, Tobacco and Firearms.

Authority

Accordingly, under the authority in 27 U.S.C. 205, 27 CFR Part 9 is amended as follows:

PART 9—AMERICAN VITICULTURAL AREAS

Paragraph 1. The table of sections in 27 CFR Part 9, Subpart C, is amended by adding the heading of § 9.102 to read as follows:

Subpart C—Approved American Viticultural Areas

Sec.

* * * * *

9.102 Sonoma Mountain.

* * * * *

Par. 2. Subpart C is amended by adding § 9.102 to read as follows:

Subpart C—Approved American Viticultural Areas

§ 9.102 Sonoma Mountain.

(a) *Name.* The name of the viticultural area described in this section is "Sonoma Mountain."

(b) *Approved maps.* The approved maps for determining the boundary of the Sonoma Mountain viticultural area are 2 U.S.G.S. topographic maps in the 7.5 minute series, as follows:

(1) Glen Ellen, Calif., dated 1954, photorevised 1980; and

(2) Kenwood, Calif., dated 1954, photorevised 1980.

(c) *Boundary.* The Sonoma Mountain viticultural area is located in Sonoma County, California. The boundary is as follows:

(1) The beginning point is the point at which the 1600-foot contour line crosses the section line dividing Section 22 from Section 23, in Township 6 North, Range 7 West.

(2) The boundary follows this section line north to the 800-foot contour line.

(3) The boundary follows the 800-foot contour line westerly, easterly, and northerly to Bennett Valley Road.

(4) The boundary follows Bennett Valley Road easterly to Enterprise Road.

(5) The boundary follows Enterprise Road southeasterly to an unnamed stream, in Section 7, Township 6 North, Range 7 West, which crosses Enterprise

Road near the point at which the road turns from an easterly to a southerly direction.

(6) The boundary follows this stream easterly to the 400-foot contour line.

(7) The boundary follows the 400-foot contour line southerly to the township line dividing Township 6 North from Township 5 North.

(8) The boundary follows a straight line extension of this township line west to the 1200-foot contour line.

(9) The boundary follows the 1200-foot contour line northwesterly to the range line dividing Range 6 West from Range 7 West.

(10) The boundary follows this range line south to the 1600-foot contour line.

(11) The boundary follows this contour line westerly to the beginning point.

Signed: December 17, 1984.

Stephen E. Higgins,

Director.

Approved: January 7, 1985.

Edward T. Stevenson,

Deputy Assistant Secretary (Operations).

[FR Doc. 85-1719 filed 1-22-85; 8:45 am]

BILLING CODE 4810-31-M

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[OPP-260049; FRL-2759-8]

Pesticide Programs; Tolerances and Exemptions From Tolerances for Pesticide Chemicals in or on Raw Agricultural Commodities; Cross-Referencing Update

AGENCY: Environmental Protection Agency (EPA).

ACTION: Rule; Cross-Referencing Update.

SUMMARY: These editorial amendments to 40 CFR Part 180 update cross-references to certain sections in 21 CFR Part 121 which were recodified.

EFFECTIVE DATE: Effective on January 23, 1985.

FOR FURTHER INFORMATION CONTACT: John A. Richards, Chief, Federal Register Staff (TS-788), Office of the Assistant Administrator for Pesticides and Toxic Substances, Environmental Protection Agency, Rm. E-603A, 401 M Street SW., Washington, D.C. 20460, (202-382-3415).

SUPPLEMENTARY INFORMATION: The Food and Drug Administration (FDA) issued a recodification of 21 CFR Part 121, Subpart B—Exemption of Certain Food Additives from the Requirement of Tolerances; Subpart C—Food Additives Permitted in Feed and Drinking Water of Animals, published in the **Federal Register** of September 10, 1976 (41 FR 38618). FDA issued a recodification of 21 CFR Part 121, Subpart D—Food Additives Permitted in Food for Human Consumption, published in the **Federal Register** of March 16, 1977 (42 FR 14302).

These regulations are cross-referenced in 40 CFR Part 180. This document amends the cross-references to reflect the new codification under 21 CFR, and represents no substantive change in the contents of the regulations under 40 CFR Part 180.

List of Subjects in 40 CFR Part 180

Administrative practice and procedures; Agricultural commodities; Pesticides and pests.

Dated: January 10, 1985.

Steven Schatzow,

Director, Office of Pesticide Programs.

PART 180—[AMENDED]

Therefore, 40 CFR Part 180 is amended as follows:

§ 180.147a [Amended]

1. In § 180.147a(b), the reference to "21 CFR 121.226" is changed to read "21 CFR 561.120".

§ 180.100 [Amended]

2. In § 180.1001(c), under the entry "Dimethylpolysiloxane", the reference to "21 CFR 121.1099" is changed to read "21 CFR 172.340".

§ 180.1025 [Amended]

3. In § 180.1025(d), the reference to "21 CFR 121.1203(b)(3)" is changed to read "21 CFR 172.250".

§ 180.1038 [Amended]

4. In § 180.1038, the reference to "21 CFR 121.2637" is changed to read "21 CFR 177.2470".

(Sec. 408, 68 Stat. 511; 21 U.S.C. 346a)

[FR Doc. 85-1577 Filed 1-22-85; 8:45 am]

BILLING CODE 6560-50-M

40 CFR Part 180

[OPP-3000103A FRL-2761-2]

Pesticide Programs; Tolerances and Exemptions From Tolerances for Pesticide Chemicals in or on Raw Agricultural Commodities; Zinc Stearate, Titanium Dioxide, and Calcium Stearate

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: These rules exempt zinc stearate, titanium dioxide, and calcium stearate from the requirement of a tolerance when used as inert ingredients in pesticide formulations used in animal ear tags. These regulations were requested by the Ralston Purina Co.

EFFECTIVE DATE: Effective on January 23, 1985.

ADDRESS: Written objections may be submitted to the: Hearing Clerk (A-110), Environmental Protection Agency, 401 M St., SW., Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT:

By mail: N. Bhushan Mandava, Registration Support and Emergency Response Branch, Environmental Protection Agency, 401 M St., SW., Washington, D.C. 20460.

Office location and telephone number: Rm. 716, CM No. 2, 1921 Jefferson Davis Highway, Arlington, VA 22202, 703-557-7700.

SUPPLEMENTARY INFORMATION: EPA issued a proposed rule, published in the **Federal Register** of October 17, 1984 (49 FR 40608), which announced that the Ralston Purina Co., St. Louis, MO 63164, had requested that 40 CFR 180.1001(e) be amended by establishing an exemption from the requirement of a tolerance for zinc stearate, titanium dioxide, and calcium stearate when used as inert ingredients in plastic ear tags for animals.

Inert ingredients are ingredients that are not active ingredients as defined in 40 CFR 162.3(c), and include, but are not limited to, the following types of ingredients (except when they have a pesticidal efficacy of their own): Solvents such as water; baits such as sugar, starches, and meat scraps; dust carriers such as talc and clay; fillers; wetting and spreading agents; propellants in aerosol dispensers; and emulsifiers. The term "inert" is not intended to imply nontoxicity; the ingredient may or may not be chemically active.

In the proposed rule, EPA stated the basis for a determination that when used in accordance with good agricultural practices, these ingredients are useful and do not pose a hazard to humans or the environment.

There were no comments or requests for referral to an advisory committee received in response to the proposed rule.

These pesticides are considered useful for the purpose for which the exemptions are sought. It is concluded that the exemptions from the requirement of a tolerance will protect the public health and are established as set forth below.

Any person adversely affected by this regulation may, within 30 days after

publication of this notice in the **Federal Register**, file written objections with the Hearing Clerk, at the address given above. Such objections should specify the provisions of the regulation deemed objectionable and the grounds for the objections. A hearing will be granted if the objections are supported by grounds legally sufficient to justify the relief sought.

The Office of Management and Budget has exempted this rule from the requirements of section 3 of Executive Order 12291.

List of Subjects in 40 CFR Part 180

Administrative practice and procedure, Agricultural commodities, Pesticides and pests.

(Sec. 408(e), 68 Stat. 514 (21 U.S.C. 346a(e))

Dated: January 11, 1985.

Susan H. Sherman,

Acting Director, Office of Pesticide Programs.

PART 180—[AMENDED]

Therefore, 40 CFR 180.1001(e) is amended by revising the entry for zinc stearate and by adding and alphabetically inserting the inert ingredients as follows:

§ 180.1001 Exemptions from the requirement of a tolerance.

* * * * *

(e) * * *

Inert ingredients	Limits	Uses
* * * * *		
Calcium stearate (CAS Reg. No. 1592-23-0).	.....	Stabilizer, component of plastic animal tag.
* * * * *		
Titanium dioxide (CAS Reg. No. 13463-67-7).	.....	Pigment/colorant in pesticide formulations for animal tag.
* * * * *		
Zinc stearate (CAS Reg. No. 557-05-1).	.....	Water repellant, desiccant, and coating agent; stabilizer, component of plastic animal tag.
* * * * *		

[FR Doc. 85-1688 Filed 1-22-85; 8:45 am]

BILLING CODE 6560-50-M

40 CFR Part 180

[00000/R716; PH-FRL 2727-1]

Pesticide Programs; Tolerances and Exemptions From Tolerances for Pesticide Chemicals in or on Raw Agricultural Commodities; Revocation of Tolerances for Ethylene Dibromide

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This rule revokes the 10 ppm tolerances in 40 CFR 180.146 for residues of inorganic bromides (calculated as Br) in or on beans (string), bitter melons (Mormodica charantia), cantaloupes, Cavendish bananas, cucumbers, guavas, litchi fruit, litchi nuts, longan fruit, peppers (bell), pineapples, and zucchini squash that have been fumigated after harvest with the insecticide ethylene dibromide (EDB) in accordance with the Mediterranean Fruit Fly Control Program or the Quarantine Program of the U.S. Department of Agriculture, and the 25 ppm tolerances for residues of total combined bromine (which includes bromine from both inorganic and organic compounds) in or on cherries and plums (fresh prunes) that have been fumigated with EDB in accordance with the above USDA programs or to meet State quarantine requirements.

EFFECTIVE DATE: Effective on January 23, 1985.

ADDRESS: Written objections may be submitted to the: Hearing Clerk, Environmental Protection Agency, Rm. M-3708 (A-110), 401 M St., SW., Washington, DC 20460.

FOR FURTHER INFORMATION CONTACT:

By mail: Richard Johnson, Registration Divison (TS-767C), Office of Pesticide Programs, 401 M St., SW., Washington, DC 20460.

Office location and telephone number: Rm. 711, Crystal Mall No. 2, 1921 Jefferson Davis Highway, Arlington, VA. 22202, (703-557-7420).

SUPPLEMENTARY INFORMATION: On August 2, 1984, EPA issued a proposed rule, published in the **Federal Register** of August 10, 1984 (49 FR 32085), which proposed the revocation of the 10 ppm tolerances in 40 CFR 180.146 for residues of inorganic bromides (calculated as Br) in or on beans (string), bitter melons (Mormodica charantia), cantaloupes, Cavendish bananas, cucumbers, guavas, litchi fruit, litchi nuts, longan fruit, peppers (bell), pineapples, and zucchini squash that have been fumigated after harvest with the insecticide ethylene dibromide (EDB) in accordance with the Mediterranean Fruit Fly Control Program or the Quarantine Program of the U.S. Department of Agriculture, and the 25 ppm tolerances for residues of total combined bromine (which includes bromine from both inorganic and organic compounds) in or on cherries and plums (fresh prunes) that have been fumigated with EDB in accordance with the above USDA programs or to meet State quarantine requirements.

No requests for referral to an advisory committee were received in response to the proposed rulemaking.

The Agency received one comment from the National Food Processors Association (NFPA). NFPA commented that the EPA proposed rule failed to recognize the fact that existing stocks of food products, to which pesticides have been legally applied prior to cancellation, may contain unavoidable residues of such pesticides. They contend that, in some cases, it may take several years for existing stocks of processed food products to pass through the distribution chain to consumers. In light of this possibility, they recommend that, after the Agency revokes a tolerance, the tolerance or an action level should continue to apply to commodities legally treated with the pesticide before the expiration date of the tolerance, and request that the Agency set forth this policy in the tolerance revocation rule. NFPA believes that such a policy would prevent recalls of legally treated food products and the associated economic consequences of such action. They also recommend that an inorganic bromide tolerance should not be revoked in the situation where a tolerance or action level is still in effect for the parent compound of a brominated fumigant in order to protect food processors from possible legal action resulting from the presence of inorganic bromide residues.

The Agency appreciates the concern expressed by the National Food Processors Association regarding the potential problem of residues of canceled pesticides in existing food stocks in a situation where the Agency revokes or amends a tolerance rule following a cancellation action. The consideration of the disposition of existing food stocks is an essential element of the Agency's decisionmaking process in such a tolerance action. No general rules, however, are applicable. The determination as to whether the presence of residues of the canceled pesticide poses a public health risk is a decision which can only be made on a case by case basis. In those situtions where the risk posed by the residues in existing stocks is insignificant, the Agency will recommend to the Food and Drug Administration that no enforcement action be taken to recall or otherwise remove those products from the market. It has generally been the policy of the Food and Drug Administration to allow existing stocks to be used up in such situations. There, however, may be situations where the risk posed by residues to the public is of sufficient concern that the Agency believes it is prudent to take measures to remove such food products bearing residues above a certain level from the consumer market. In appropriate situations, the Agency will recommend to FDA that an action level be

established below which FDA will exercise its discretion not to take enforcement action against existing stocks of the residue-bearing products.

NFPA did not supply the Agency with any specific data or information which would lead the Agency to conclude that there is a significant stock of processed fruits and vegetables containing EDB residues in the marketplace. Accordingly, the Agency believes there is no basis at this time for recommending that the FDA set action levels for any of the fruit and vegetable commodities enumerated in this rule.

With regard to the concern expressed by NFPA regarding inorganic bromide residues, the Agency discussed its policy about such residues in the final rules revoking the inorganic bromide tolerance for EDB in or on citrus fruits and papayas (49 FR 22082, May 25, 1984) and establishing a tolerance for EDB *per se* in or on these commodities (49 FR 22083, May 25, 1984). To summarize, in establishing a tolerance for residues of a pesticide expected to result from a particular use of that pesticide, the Agency identifies the residues of concern and specifies the levels at which those residues are to be regulated. The presence in the food of any other substance, whether parent compound, degradation product or metabolite, resulting from a registered pesticide use, which is not included in the definition of the residue to be regulated, is not an appropriate basis for enforcement action. The Food and Drug Administration's tolerance enforcement procedures are consistent with this policy.

As discussed in the proposal published on August 10, 1984, the Agency previously issued a notice of intent to cancel registrations of EDB for the quarantine fumigation of fruits and vegetables which was published in the **Federal Register** of October 11, 1983 (48 FR 46234). This cancellation became effective for the fruits and vegetables enumerated in this Notice on September 1, 1984.

For those examining Part 180 of Chapter 40 of the Code of Federal Regulations (CFR), it should be noted that in the **Federal Register** of April 23, 1984 (49 FR 17147), 40 CFR 180.146 was amended by deleting the first paragraph listing tolerances at 50 ppm for various grains calculated as the inorganic bromide molecule.

Based on the information considered by the Agency, and discussed in detail in the August 10 **Federal Register** proposal and the support document which is available from the Agency at the address given in **"FOR FURTHER INFORMATION"** above, and after consideration of the comments submitted to the docket, the Agency is hereby revoking the tolerances in 40 CFR 180.146 for residues of inorganic bromides (calculted as Br) in or on beans (string), bitter melons (*Mormodica charantia*), cantaloupes, Cavendish bananas, cucumbers, guavas, litchi fruit, litchi nuts, longan fruit, peppers (bell), pineapples, and zucchini squash that have been fumigated after harvest with EDB in accordance with the USDA programs enumerated above and for residues of total combined bromine (which includes bromine from both inorganic and organic compounds) in or on cherries and plums (fresh prunes) that have been fumigated in accordance with the above USDA programs or to meet state quarantine requirements.

The Agency has recently issued in the **Federal Register** a final rule [00000/R715] revoking the 10 ppm tolerance in 40 CFR 180.146 for residues of inorganic bromide (calculated as Br) in or on mangoes that have been fumigated after harvest with EDB in accordance with the Mediterranean Fruit Fly Control Program or the Quarantine Program of the U.S. Department of Agriculture, and a final rule establishing a tolerance of 30 ppb (.03 ppm) for residues of EDB *per se* in the edible pulp of mangoes resulting from fumigation after harvest in accordance with the Mediterranean Fruit Fly Control Program or the Quarantine Program of the U.S. Department of Agriculture, with a termination date of September 1, 1985.

Any person adversely affected by this regulation revoking the tolerances in 40 CFR 180.146 for residues of inorganic bromides (calculated as Br) in or on beans (string), bitter melons (Mormodica charantia), cantaloupes, Cavendish bananas, cucumbers, guavas, litchi fruit, litchi nuts, longan fruit, peppers (bell), pineapples, and zucchini squash that have been fumigated after harvest with EDB in accordance with the Mediterranean Fruit Fly Control Program or the Quarantine Program of the U.S. Department of Agriculture, and for residues of total combined bromine (which includes bromine from both inorganic and organic compounds) in or on cherries and plums (fresh prunes) that have been fumigated after harvest with EDB in accordance with the above USDA programs or to meet state quarantine requirements, may, within 30 days after the date of publication of this regulation in the **Federal Register**, file written objections with the Hearing Clerk, at the address given below. Such objections must be submitted in quintuplicate and specify the provisions of the regulation deemed objectionable and the grounds for the objections. If a hearing is requested, the objections must state the issues for the hearing. A hearing will be granted if the objections are supported by grounds legally sufficient to justify the relief sought.

This document has been sent to the Office of Management and Budget for review as required by section 3 of Executive Order 12291.

In order to satisfy requirements for analysis as specified by Executive Order 12291, the Regulatory Flexibility Act and the Paperwork Reduction Act, the Agency has analyzed the costs and benefits of the revocation of the tolerances in 40 CFR 180.146 for residues of inorganic bromides (calculated as Br) in or on the fruits and vegetables enumerated in this Notice that have been fumigated with EDB after harvest. Documents containing these analyses are available at the address identified elsewhere in this Notice.

As explained in the proposal published on August 10, 1984, pursuant to the requirements of Executive Order 12291, the Agency has determined that this tolerance revocation action is not expected to significantly affect the prices or overall production levels of the commodities enumerated in this Notice.

This rulemaking has been reviewed under the Regulatory Flexibility Act of 1980 (Pub. L. 96–354; 94 Stat. 1164, 5 U.S.C. 601 *et seq.*) and it has been determined that it will not have a significant economic impact on a substantial number of small businesses, small governments, or small organizations. The reasons for this conclusion are discussed in detail in the August 10, 1984 proposal and the support document available from the Agency at the address given above.

This rule does not contain any information collection requirements subject to OMB review under the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.*

(Sec. 408(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a(m)))

List of Subjects in 40 CFR Part 180

Administrative practice and procedures, Agricultural commodities, Pesticides and pests.

Dated: January 10, 1985.

Lee M. Thomas,
Acting Administrator.

PART 180—[AMENDED]

§ 180.146 [Removed]

Therefore, 40 CFR 180.146 is removed.

[FR Doc. 85–1683 Filed 1–22–85; 8:45 am]
BILLING CODE 6560–50–M

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40 CFR Part 180

[OPP–3000105A; FRL–2761–4]

Pesticide Programs; Tolerances and Exemptions From Tolerances for Pesticide Chemicals in or on Raw Agricultural Commodities; Mono- and Bis-Perfluoroalkyl Phosphates

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This rule exempts mono- and bis-(1H, 1H, 2H, 2H-perfluoroalkyl) phosphates where the alkyl group is even numbered in the C_6–C_{12} range from the requirement of a tolerance when used as a defoaming agent in pesticide formulations. This regulation was requested by the American Hoechst Corp.

EFFECTIVE DATE: Effective on January 23, 1985.

ADDRESS: Written objections may be submitted to the: Hearing Clerk (A–110), Environmental Protection Agency, 401 M St., SW., Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT:

By mail: N. Bhushan Mandava, Registration Support and Emergency Response Branch, Environmental Protection Agency, 401 M St., SW., Washington, D.C. 20460.

Office location and telephone number: Rm. 716, CM #2, 1921 Jefferson Davis Highway, Arlington, VA 22202, 703–557–7700.

SUPPLEMENTARY INFORMATION: EPA issued a proposed rule, published in the **Federal Register** of October 24, 1984 (49 FR 42758), which announced that American Hoechst Corp., Somerville, NJ 08876, had requested that 40 CFR 180.1001(d) be amended by establishing an exemption from the requirement of a tolerance for mono- and bis-(1H, 1H, 2H-perfluoroalkyl) phosphates where the alkyl group is even numbered in the C_6–C_{12} range when used as a defoaming agent in pesticide formulations applied to growing crops only.

Inert ingredients are ingredients that are not active ingredients as defined in 40 CFR 162.3(c), and include, but are not limited to, the following types of ingredients (except when they have a pesticidal efficacy of their own): Solvents such as water; baits such as sugar, starches, and meat scraps; dust carriers such as talc and clay; fillers; wetting and spreading agents; propellants in aerosol dispensers; and emulsifiers. The term "inert" is not intended to imply nontoxicity; the ingredient may or may not be chemically active.

In the proposed rule, EPA stated the basis for a determination that when used in accordance with good agricultural practices, these ingredients are useful and do not pose a hazard to humans or the environment.

There were no comments or requests for referral to an advisory committee received in response to the proposed rule.

These pesticides are considered useful for the purpose for which the exemptions are sought. It is concluded that the exemption from the requirement of a tolerance will protect the public health and is established as set forth below.

Any person adversely affected by this regulation may, within 30 days after publication of this notice in the **Federal Register**, file written objections with the Hearing Clerk, at the address given above. Such objections should specify the provisions of the regulation deemed objectionable and the grounds for the objections. A hearing will be granted if the objections are supported by grounds legally sufficient to justify the relief sought.

The Office of Management and Budget has exempted this rule from the requirements of section 3 of Executive Order 12291.

List of Subjects in 40 CFR Part 180

Administrative practice and procedure, Agricultural commodities, Pesticides and pests.

(Sec. 408(e), 68 Stat. 514 (21 U.S.C. 346a(e))

Dated: January 11, 1985.

Susan H. Sherman,
Acting Director, Office of Pesticide Programs.

PART 180—[AMENDED]

Therefore, 40 CFR 180.1001(d) is amended by adding and alphabetically inserting the inert ingredients as follows:

§ 180.1001 Exemptions from the requirement of a tolerance.

* * * * *

(d) * * *

Inert ingredients	Limits	Uses
* * * * *		
Mono- and Bis-(1H, 1H, 2H, 2H-perfluoroalkyl) phosphates where the alkyl group is even numbered and in the C_6–C_{12} range.	Not more than 0.5% of pesticide formulation.	Defoaming agent
* * * * *		

[FR Doc. 85–1686 Filed 1–22–85; 8:45 am]
BILLING CODE 6560–50–M

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40 CFR Part 180

[OPP–3000104A; FRL–2761–5]

Pesticide Programs; Tolerances and Exemptions From Tolerances for Pesticide Chemicals in or on Raw Agricultural Commodities; Methyl N-Amyl Ketone

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This rule exempts methyl *n*-amyl ketone from the requirement of a tolerance when used as a solvent, cosolvent in pesticide formulations. This regulation was requested by the Eastman Kodak Co.

EFFECTIVE DATE: Effective on January 23, 1985.

ADDRESS: Written objections may be submitted to the: Hearing Clerk (A–110), Environmental Protection Agency, 401 M St., SW., Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT:

By mail: N. Bhushan Mandava, Registration Support and Emergency Response Branch, Environmental Protection Agency, 401 M. St., SW., Washington, D.C. 20460.

Office location and telephone number: Rm. 716, CM #2, 1921 Jefferson Davis Highway, Arlington, VA 22202, 703–557–7700.

SUPPLEMENTARY INFORMATION: EPA issued a proposed rule, published in the **Federal Register** of October 24, 1984 (49 FR 42757), which announced that the Eastman Kodak Co., Kingsport, TN 37662, had requested that 40 CFR 180.1001 (c) and (e) be amended by establishing an exemption from the requirement of a tolerance for methyl *n*-amyl ketone when used as a solvent, cosolvent in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest or to animals.

Inert ingredients are ingredients that are not active ingredients as defined in 40 CFR 162.3(c), and include, but are not

limited to, the following types of ingredients (except when they have a pesticidal efficacy of their own): Solvents such as water; baits such as sugar, starches, and meat scraps; dust carriers such as talc and clay; fillers; wetting and spreading agents; propellants in aerosol dispensers; and emulsifiers. The term "inert" is not intended to imply nontoxicity; the ingredient may or may not be chemically active.

In the proposed rule, EPA stated the basis for a determination that when used in accordance with good agricultural practices, the ingredient is useful and does not pose a hazard to humans or the environment.

There were no comments or requests for referral to an advisory committee received in response to the proposed rule.

The pesticide is considered useful for the purpose for which the exemption is sought. It is concluded that the exemption from the requirement of a tolerance will protect the public health and is established as set forth below.

Any person adversely affected by this regulation may, within 30 days after publication of this notice in the **Federal Register**, file written objections with the Hearing Clerk, at the address given above. Such objections should specify the provisions of the regulation deemed objectionable and the grounds for the objections. A hearing will be granted if the objections are supported by grounds legally sufficient to justify the relief sought.

The Office of Management and Budget has exempted this rule from the requirements of section 3 of Executive Order 12291.

(Sec. 408(e), 68 Stat. 514 (21 U.S.C. 346a(e)))

List of Subjects in 40 CFR Part 180

Administrative practice and procedure, Agricultural commodities, Pesticides and pests.

Dated: January 11, 1985.

Susan H. Sherman,

Acting Director, Office of Pesticide Programs.

PART 180—[AMENDED]

Therefore, 40 CFR 180.1001 (c) and (e) are amended by adding and alphabetically inserting the inert ingredient as follows:

§ 180.1001 Exemptions from the requirement of a tolerance.

* * * * *

(c) * * *

Inert ingredients	Limits	Uses
* * * * *		
Methyl *n*-amyl ketone (CAS Reg. No. 110-43-0).	.....	Solvent, cosolvent.
* * * * *		

* * * * *

(e) * * *

Inert ingredients	Limits	Uses
* * * * *		
Methyl *n*-amyl ketone (CAS Reg. No. 110-43-0).	.....	Solvent, cosolvent.
* * * * *		

[FR Doc. 85-1685 Filed 1-22-85; 8:45 am]

BILLING CODE 6560-50-M

FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 0

[FCC 84-642]

Establishment of the Office of Congressional and Public Affairs

AGENCY: Federal Communications Commission.

ACTION: Final rule.

SUMMARY: This action reorganizes the Office of Public Affairs.

To most effectively manage and operate the Commission's public information program, the Federal Communications Commission has moved to merge the Office of Public Affairs, the Legislative Affairs Staff of the Office of General Counsel, and the Congressional Correspondence Staff of the Office of the Chairman.

This action will create a new office to provide an integrated organizational structure for communicating the Commission's policies regarding telecommunications to the Congress, the news media and the public.

EFFECTIVE DATE: December 10, 1984.

ADDRESS: Federal Communications Commission, Washington, D.C. 20554.

FOR FURTHER INFORMATION CONTACT: Maureen Peratino, Office of Congressional and Public Affairs (202) 254-7674.

SUPPLEMENTARY INFORMATION:

List of Subjects in 47 CFR Part 0

Organization and functions (Government agencies).

Order

In the matter of amendment of Part 0 of the Commission's Rules to Establish the Office of Congressional and Public Affairs.

Adopted: November 15, 1984.

Released: December 27, 1984.

By the Commission: Commissioner Rivera concurring in the result.

1. The Commission has before it for consideration the consolidation of the Office of Public Affairs with the legislative affairs function of the Office of General Counsel and the congressional correspondence function of the Office of the Chairman. Implementation of the proposed changes would require revision of §§ 0.5, 0.15, 0.16 and 0.41, plus the unnumbered, centered title between §§ 0.12 and 0.15 of the Commission's Rules and Regulations.

2. To reflect an increasing commitment by the Commission to coordinating telecommunications policy considerations with the Congress, the Commission is hereby approving the consolidation of the Office of Public Affairs, the legislative affairs functions of the Office of General Counsel and the congressional correspondence functions of the Office of the Chairman into the Office of Congressional and Public Affairs. This reorganization creates an integrated organizational structure for communicating the Commission's policies regarding telecommunications to the Congress, the news media and the public, by combining these similar activities into a single bureau level entity. Also, this reorganization recognizes, by elevating the Congressional affairs function to the bureau level, the importance of policy coordination between the Commission and Congress.

3. The amendments adopted herein pertain to agency organization. The prior notice procedure and effective date provisions of section 4 of the Administrative Procedure Act are therefore, inapplicable. Authority for the amendments adopted herein are contained in sections 4(i) and 5(b) of the Communications Act of 1934, as amended.

4. In view of the foregoing, it is ordered, effective December 10, 1984, that Part 0 of the Rules and Regulations is amended as set forth in the Appendix hereto.

(Secs. 4, 303, 48 Stat., as amended, 1066, 1082; 47 U.S.C. 154, 303)

Federal Communications Commission.

William J. Tricarico,

Secretary.

Appendix

Part 0 of Chapter 1 of Title 47 of the Code of Federal Regulations is hereby amended as indicated below:

1. Section 0.5 of the Commission Rules and Regulations is amended by adding

paragraph (a)(14) and revising paragraph (b)(7) to read as follows:

§ 0.5 General description of Commission Organization and Operation.

* * * * *

(a) * * *

(14) Office of Congressional and Public Affairs

(b) * * *

(7) Office of Congressional and Public Affairs. The Office of Congressional and Public Affairs has primary responsibility for the Commission's News Media, Consumer Assistance and Small Business, and Legislative Affairs programs. The major purpose of these programs is to inform the public of the Commission's regulatory requirements, to facilitate public participation in the Commission's decisionmaking processes, to apprise the public of Commission policies promoting minority participation in telecommunications and to implement the Commission's legislative programs in the telecommunications industry.

* * * * *

2. The unnumbered, centered title between § 0.12 and § 0.15 of the Commission's Rules is revised to read as follows: "Office of Congressional and Public Affairs."

3. Section 0.15 of the Commission's Rules and Regulations is amended by revising the introductory paragraph and adding a new paragraph (j) to read as follows:

§ 0.15 Functions of the Office.

The Office of Congressional and Public Affairs is directly responsible to the Commission. The Office has the following duties and responsibilities:

* * * * *

(j) Advise and make recommendations to the Commission with respect to legislation proposed by members of Congress and coordinate the preparation of Commission views thereon for submission to Congress. Coordinate with the Office of General Counsel reponses to Congressional inquiries as to the local ramifications of Commission policies, regulations, rules and statutory interpretations. Assist the Office of Managing Director in preparation of the annual report to Congress, the Commission budget and appropriations legislation to Congress. Assist the Chairman in preparation for, and the coordination of the Chairman's appearances before the Committees of Congress. Coordinate the Commission annual legislation program. Coordinate Commission and staff responses to inquiries by individual members of Congress, congressional committees and staffs.

4. Section 0.16 is revised to read:

§ 0.16 Units in the Office.

The Office of Congressional and Public Affairs is comprised of the following units:

(a) Immediate Office of the Director.

(b) Consumer Assistance and Small Business Division.

(c) News Media Division.

(d) Legislative Affairs Division.

5. Section 0.41 is amended by revising paragraph (b) as follows:

§ 0.41 Functions of the Office.

* * * * *

(b) To advise and make recommendations to the Commission with respect to proposed legislation and submit agency views on legislation when appropriate.

* * * * *

[FR Doc. 85-1610 Filed 1-22-85; 8:45 am]

BILLING CODE 6712-01-M

INTERSTATE COMMERCE COMMISSION

49 CFR Part 1011

Commission Issuances; Conferences on Significant Commission Proceedings Involving Major Transportation Issues

AGENCY: Interstate Commerce Commission.

ACTION: Final rules.

SUMMARY: By notice published in the **Federal Register** at 49 FR 20954, May 17, 1984, the Commission announced a new procedure for voting on significant cases. The new procedure is contained in Issuance 11. Conferences, (Issuance 11 hereafter). It specifies that Commission conference shall be convened for the purpose of voting on significant Commission proceedings involving major transportation issues.

In this document, the Commission announces changes to the Commission's organizational rules in 49 CFR Part 1011—Commission Organization: Delegations of Authority, which will integrate our existing regulations governing Commission conferences. Also, changes are being made to Issuance 11 so that it will be internally consistent.

EFFECTIVE DATE: January 23, 1985.

FOR FURTHER INFORMATION CONTACT: Kathleen M. King, (202) 275-7429.

SUPPLEMENTARY INFORMATION: The following are amendments to the Commission's organizational rules contained in 49 CFR Part 1011 and the Commission Issuances of December 19, 1978 (43 FR 57211, December 6, 1978), which contain the Commission's internal operating procedures. These changes complete implementation of the Commission's new voting procedures initially adopted on May 10, 1984. The new procedures provide for voting on significant Commission proceedings, involving major transportation issues, at Commission conferences, rather than through notation voting.

The amendments to 49 CFR 1011.4(c)(2) set forth in Appendix A will add the new voting procedures to our organizational rules. The new language is consistent with the language which appears in item 11(f) of revised Issuance 11.

Additional language is being added in Issuance 11 so that the issuance will be internally consistent. The new language which will appear in item 11(e) of Issuance 11 reads as follows: "These procedures shall also apply to item 11(f) conferences." The revised text of items 11(e) and 11(f) are set forth in Appendix B.

Since this document governs the internal operations and procedures of the Commission, it is being issued in final form. Public comments are not being requested.

This decision does not significantly affect the quality of the human environment or energy conservation.

List of Subjects in 49 CFR Part 1011

Administrative practice and procedure, Organization and functions.

Authority: 49 U.S.C. 10301 and 10321(a).

Decided: January 14, 1985.

By the Commission, Chairman Taylor, Vice Chairman Gradison, Commissioners Sterrett, Andre, Simmons, Lamboley and Strenio.

James H. Bayne,

Secretary.

Appendix A

PART 1011—COMMISSION ORGANIZATION: DELEGATIONS OF AUTHORITY

49 CFR Part 1011 is amended by revising § 1011. 4(c)(2) to read as follows:

§ 1011.4 The Chairman, Vice Chairman, and Senior Commissioner present.

* * * * *

(c) * * *

(2) Except regular sessions, which are provided for by regulations prescribed by the Commission, the Chairman may call the Commission into special session whenever in his or her opinion any matter or business of the Commission so requires. The Chairman shall convene a special session for consideration of any

matter or business upon request or a member of the Commission unless a majority of the Commission votes not to hold a special session, or to delay conference consideration of that item, or unless the Chairman finds that special circumstances warrant a delay. Notwithstanding the first two sentences of this paragraph, upon the written request of any member of the Commission, the Chairman shall schedule a Commission conference for the purpose of discussing and voting upon significant Commission proceedings involving major transportation issues, and such conference shall be held within a reasonable time following the close of the record in the proceeding involved.

* * * * *

Appendix B

11. *Conferences.*

(e) *Delayed voting.*—In cases where a majority has voted to take a particular action, a member may, with the approval of the majority, withhold his or her vote and vote by written memorandum within a time agreed to by the majority. In such a case, the date of the conference shall be the date of the action. If the member fails to vote within an allotted time, he or she shall be shown as not participating. Where voting at a conference is indecisive, and one or more members wishes to delay voting, the matter shall either be rescheduled for a future conference or, if there is no objection, transferred to the notation voting calendar. These procedures shall also apply to item 11(f) conferences.

(f) *Commission Conferences on Significant Proceedings Involving Major Transportation Issues.*

(1) Commission conferences shall be convened by the Chairman for the purpose of discussing and voting upon significant Commission proceedings involving major transportation issues.

(2) Notwithstanding sections 11(b)(2), 11(c) (1) and (2), upon the written request of any member of the Commission, the Chairman shall schedule a Commission conference for the purpose set forth in paragraph (1), and such conference shall be held within a reasonable period following the close of the record in the proceeding involved.

(3) No meeting will be formally noticed under section 552b(e] until two working days after the receipt by each Commissioner of the staff drafts or option papers that are to be considered at the proposed meeting.

[FR Doc. 85–1692 Filed 1–22–85; 8:45 am]
BILLING CODE 7035-01-M

Proposed Rules

Federal Register
Vol. 50, No. 15
Wednesday, January 23, 1985

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF TRANSPORTATION

Federal Aviation Administration

14 CFR Part 71

[Airspace Docket No. 84-AAL-15]

Proposed Alteration of Additional Control Area 1485, AK

Correction

In FR Doc. 85-939, beginning on page 1867 in the issue of Monday, January 14, 1985, make the following correction:

On page 1869, first column, sixth line under the heading **Control 1485—[Revised]**, "71°00′ 00″ N." should have read "72°00′ 00″ N.".

BILLING CODE 1505-01-M

DELAWARE RIVER BASIN COMMISSION

18 CFR Part 430

Revised Proposed Amendments to Ground Water Protected Area; Pennsylvania

AGENCY: Delaware River Basin Commission.

ACTION: Revision of proposed rules and public hearing.

SUMMARY: Notice is hereby given that the Delaware River Basin Commission will hold a public hearing on revised proposed amendments to the Ground Water Protected Area Regulations for Southeastern Pennsylvania. The hearing will be a part of the Commission's regular business meeting which is open to the public. Please see the Notices section of today's issue of the **Federal Register** for Notice of the other subjects of the hearing.

A public hearing was held on proposed amendments to the Commission's Ground Water Protected Area Regulations on October 24, 1984 in Philadelphia, Pennsylvania as noticed in the October 16, 1984 **Federal Register**, Vol. 49, No. 201, pages 40434 and 40435. Notice was provided in the November 2, 1984 **Federal Register**, Vol. 49, No. 214, page 44105, that the Commission had extended the comment period to November 15, 1984 on those proposed amendments.

Based upon comments received and further careful consideration, the Commission is now revising the proposed amendments as published herein, subject to public hearing.

DATES: The public hearing is scheduled for Wednesday, January 30, 1985, beginning at 1:30 p.m. Persons wishing to testify at this hearing are requested to register with the Secretary prior to the hearing. The comment closing date will be announced at the hearing.

ADDRESSES: Written comments should be submitted to Susan M. Weisman, Delaware River Basin Commission, P.O. Box 7360, West Trenton, New Jersey 08628. The public hearing will be held in the Goddard Conference Room of the Commission's Offices at 25 State Police Drive, West Trenton, New Jersey.

FOR FURTHER INFORMATION CONTACT: Susan M. Weisman, Commission Secretary, Delaware River Basin Commission, Telephone (609) 883-9500.

List of Subjects in 18 CFR Part 430

Water supply.

PART 430—[AMENDED]

The revised proposed amendments to the Commission's Ground Water Protected Area Regulations for Southeastern Pennsylvania consist of the addition of two new paragraphs (e) and (f) to § 430.13. The existing paragraph (e) of the Ground Water Protected Area Regulations is to be redesignated as (g). The new paragraphs (e) and (f) would be added to read as follows:

§ 430.13 Protected area permits for new withdrawals.

* * * * *

(e) Ground water withdrawals for space heating or cooling purposes that are less than 100,000 gallons per day shall be exempt from obtaining a protected area permit provided that the water withdrawn is returned locally, and to the same ground water basin and aquifer system from which it is withdrawn, undiminished in quantity and quality (except temperature). Ground water withdrawals for space heating or cooling that are subsequently used for commercial or industrial water supply purposes are subject to Commission withdrawal and wastewater discharge regulations. Ground water withdrawals exempted pursuant to this subsection shall be subject to the registration requirements of 18 CFR 430.17.

(f) All ground water withdrawal projects exempted by paragraph (e) of this section shall be constructed in conformance with accepted industry practice and as a minimum shall comply with the following standards:

(1) All wells shall be drilled by a Pennsylvania licensed well driller and a Water Well Inventory Report shall be completed and filed with Topographic and Geologic Survey, PADER;

(2) No wells shall be located within a 100-year floodway;

(3) All wells shall have top of casing extended a minimum of one foot above the 100-year flood elevation;

(4) All wells shall have the casing protruding a minimum of six inches above the immediate surrounding grade;

(5) The area around all wells or well pits shall be constructed and/or graded to prevent the entrance of surface waters;

(6) All wells shall be accessible for inspection and shall have an access hole for water level measurements;

(7) All ground water heat pump systems shall be equipped with an automatic shutdown device in case of a leak in the refrigeration system;

(8) Any drilled well holes that are abandoned shall be sealed with a minimum of ten feet of cement grout. Additional seals may be required to separate different water-bearing zones.

(Delaware River Basin Compact (75 Stat. 688))

Susan M. Weisman,

Secretary.

[FR Doc. 85-1673 Filed 1-22-85; 8:45 am]

BILLING CODE 6360-01-M

DEPARTMENT OF THE INTERIOR

Office of Surface Mining Reclamation and Enforcement

30 CFR Part 901

Surface Coal Mining and Reclamation Operations on Federal Lands Under the Permanent Program; State-Federal Cooperative Agreements; Alabama

AGENCY: Office of Surface Mining Reclamation and Enforcement (OSM), Interior.

ACTION: Proposed rule.

SUMMARY: The Office of Surface Mining Reclamation and Enforcement (OSM) is proposing to adopt a cooperative agreement between the Department of the Interior and the State of Alabama for the regulation of surface coal mining and reclamation operations on Federal lands in Alabama under the permanent regulatory program. Such a cooperative agreement is provided for by the Surface Mining Control and Reclamation Act of 1977. This notice of proposed rulemaking provides additional information on the proposed terms of the cooperative agreement and other issues.

DATES: The public comment period on this proposed rule will extend until February 22, 1985. The public hearing will be held at the location shown in **"ADDRESSES"** below, on February 18, 1985. Any person interested in making an oral or written presentation at the hearing must contact OSM at the address and phone number listed under **"FOR FURTHER INFORMATION CONTACT"** by February 12, 1985.

ADDRESSES: Written comments must be mailed to:

Administrative Record, Office of Surface Mining, Room 5315–L, 1951 Constitution Avenue NW., Washington, D.C. 20240

Written comments may also be hand-delivered to: Office of Surface Mining, Administrative Record, Room 5315, 1100 L Street, NW., Washington, D.C. 20005.

Copies of the proposed agreement and of the related information required under 30 CFR Part 745 are available for inspection Monday through Friday, 8:30 a.m. to 4 p.m., excluding holidays, at the following addresses:

Alabama Surface Mining Commission, Central Bank Building, Second Floor, 811 Second Avenue, Jasper, Alabama

Office of Surface Mining, Room 5315, 1100 L Street, NW., Washington, D.C.

The public hearing will be held at the Office of Surface Mining, Birmingham Field Office, 228 West Valley Avenue, Homewood, Alabama, beginning at 9 AM. If no one has contacted OSM by February 12, 1985 to express an interest in testifying at the hearing, it will not be held. Persons interested in attending the hearing but not testifying should contact OSM at the address and phone number listed under **"FOR FURTHER INFORMATION CONTACT"** prior to the scheduled hearing date to see if the hearing has been cancelled.

FOR FURTHER INFORMATION CONTACT: Murray Newton, Chief, Branch of Regulatory Programs, Office of Surface Mining, 1951 Constitution Avenue, NW., Washington, D.C. 20240, Telephone: (202) 343–5866.

SUPPLEMENTARY INFORMATION: The preamble to the proposed rulemaking is divided into four parts as follows:

I. Public Comment Procedures
II. The State of Alabama's Application
III. Summary of the Terms of the Proposed Cooperative Agreement
IV. Procedural Matters

I. Public Comment Procedures

A. Public Hearing

The hearing will begin at 9:00 AM and continue until all persons then in attendance wishing to testify have done so.

Individual testimony at the public hearing will be limited to 15 minutes. The hearing will be transcribed by a court reporter. Filing of a written statement at the time of giving oral testimony would facilitate the job of the court reporter. Submission of written statements in advance of the hearing would greatly assist OSM officials who will attend the hearing by providing an opportunity to consider appropriate questions which could be asked for clarification or to request more specific information from the person testifying.

B. Public Meetings

Representatives of OSM will be available to meet during the comment period at the request of members of the public to receive their recommendations and comments concerning the proposed cooperative agreement. Persons wishing to schedule such meetings should contact the individual listed under **"FOR FURTHER INFORMATION CONTACT."** OSM representatives will be available for these meetings between 9 AM and 4 PM local time, Monday through Friday, excluding holidays. All such meetings will be open to the public.

C. Contacts With State Representatives

The Department has previously announced (45 FR 58378; September 3, 1980) its intention to follow the "Guidelines for Contacts with Employees and Officials During Consideration of State Permanent Regulatory Programs" published at 44 FR 54444 (September 19, 1979), during the process of developing cooperative agreements with the States. As written, the guidelines apply only to the State program review and decision process. However, the Department believes that the guidelines should also be applied in the development of State-Federal permanent program cooperative agreements because of the close interrelationship between each cooperative agreement and the approved State Program. The need to preserve the ability of the Department and the State to work together through the stages of the cooperative agreement and the right of the public to be informed and to have the opportunity to comment meaningfully on issues raised are both principles applicable to permanent program cooperative agreement rulemakings.

(This decision required that minor changes in the guidelines be made to clarify their applicability to cooperative agreement rulemakings. Accordingly, revised guidelines for contacts with Department employees and officials during permanent program cooperative agreement rulemaking are given below. See the notice of September 19, 1979, 44 FR 54444, for a full discussion of the guidelines and supporting principles. The September 19, 1979, guidelines remain fully applicable to the State program review process.

1. Upon request the Department will meet with any member of the public through the end of the public comment period. Notices of scheduled meetings will be posted in a public place. The meetings will be open.

2. The Department will meet the State representatives or have telephone conversations with them, upon the initiative of either party, up to the point of the Secretary's decision to enter into a permanent program cooperative agreement with a State. These meetings will be open to the public unless the Department decides an executive session is appropriate. Advance notice of scheduled meetings will be posted in a public place. Notice of the executive session will be posted in a public place.

3. The Department will keep a summary record of all meetings and discussions, whether in person or by telephone, on a proposed cooperative agreement. This record will include a summary of the discussion and a list of all written information OSM receives. All such records along with all written communications relating to the cooperative agreement shall be made available to the public.

4. In those instances where the Department has conducted meetings or discussion with a State after the close of the public comment period, the Department will include summaries of the meetings in the record and, if necessary to assure an effective opportunity for public participation, provide an opportunity for the public to review the record of such meetings and discussions and to comment on them before a decision is made to enter into a permanent program cooperative agreement.

D. Public Comments

Written an oral comments should be as specific as possible. Although all comments are invited, those most likely to influence decisions on the cooperative agreement will be those which are supported by reasoning.

All written comments must be received by OSM by 5:00 PM local time on the date the comment period closes. OSM cannot ensure that written comments received after the close of the comment period or delivered during the comment period to locations other than those specified above will be considered and included in the administrative record. Notices of meetings, summaries of all meetings and telephone conversations, all public comments received, and a transcript of the public hearing will be made available for public review at the Office of Surface Mining address noted above.

II. The State of Alabama's Application

On July 20, 1984, Alabama submitted a proposed permanent program cooperative agreement between the Department of the Interior and the State of Alabama which would make Alabama the regulatory authority for the regulation of surface coal mining and reclamation operations on Federal lands in that State. The purpose of this notice is to begin the rulemaking process for adopting such a cooperative agreement.

Section 523(c) of the Surface Mining Control and Reclamation Act of 1977 (SMCRA or the Act), 30 U.S.C. 1201 *et seq.*, and the implementing regulations at 30 CFR Part 745 allow a State and the Secretary of the Interior to enter into a permanent program cooperative agreement if the State has an approved State program for the regulation of surface coal mining and reclamation operations on non-Federal and non-Indian lands. Permanent program cooperative agreements are authorized by the first sentence of section 523(c), which provides that "[a]ny State with an approved State program may elect to enter into a cooperative agreement with the Secretary to provide for State regulation of surface coal mining and reclamation operations on Federal lands within the State, provided the Secretary determines in writing that such State has the necessary personnel and funding to fully implement such a cooperative agreement in accordance with the provision of this Act." 30 U.S.C. 1273(c).

The requirements for States to elect to enter into permanent program cooperative agreements are found in 30 CFR Part 745. For recent amendments of these rules, see 48 FR 6912 (February 16, 1983). Sections 745.11 (b) and (f) of the regulations require that certain information relating to a State's ability to administer a cooperative agreement in accordance with the Act be submitted with a request for a permanent program cooperative agreement, except to the extent that the information has previously been included in the approved State Program.

Alabama satisfied the requirements of 30 CFR 745.11(f)(1) when it obtained approval of its State Program on July 5, 1984 (49 FR 27500). The information required in 30 CFR 745.11(b)(1) and 30 CFR 745.11(f)(2) was included in Alabama's request for approval of its State Program and in subsequent requests for administrative and enforcement funding under 30 CFR Part 735. The information relating to Alabama's authority to enter into the cooperative agreement was provided in a letter from the Attorney General dated September 10, 1984, in which the Attorney General stated that there exists no statutory, regulatory, or legal constraint within the State of Alabama which would preclude the Alabama regulatory authority from fully carrying out the provisions of the agreement.

III. Summary of the Terms of the Proposed Cooperative Agreement

A summary of the proposed cooperative agreement appears below. OSM emphasizes that the proposed permanent program cooperative agreement is subject to further change because of public comments and/or further discussion with the state of Alabama.

The nature and extent of the Secretary's ability to delegate authority on Federal Lands to States through cooperative agreements was a subject of a recent Federal District Court opinion in *In Re: Permanent Surface Mining Litigation II*, Civil Action No. 79-1144 (D.D.C.; July 6, 1984). The Alabama cooperative agreement proposed here is consistent with that decision.

Article I: Introduction, Purpose, and Responsible Agencies

Article I would set forth the legal authority for the cooperative agreement which is contained in section 523(c) of the Surface Mining Control and Reclamation Act (Federal Act or Act). The purposes of the agreement and designation of the responsible administrative agencies of the Department and of the State are also included in Article I.

Article II: Effective Date

Article II povides that the cooperative agreement would be effective after it has been signed by the Secretary and the Governor, and 30 days after publication as a final rule in the **Federal Register.** It would remain in effect until terminated as provided in Article XI.

Article III: Definitions

Article III would provide that any terms and phrases used in the agreement be given the same meanings as set forth in the Federal and State Acts, regulations promulgated pursuant to those Acts, 30 CFR Parts 700, 701, and 740, and the approved State Program. Defining terms and phrases in this manner would ensure consistency between applicable regulations and the agreement. Where there are conflicts in definitions, those included in the approved State Program would apply, except where the term being defined related to those responsibilities of the Secretary that cannot be assumed by the State under the agreement.

Article IV: Applicablility

Article IV would state that the laws, regulations, terms, and conditions of Alabama's approved State Program are applicable to surface coal mining and reclamation operations on Federal lands in Alabama except as otherwise stated in the cooperative agreement, the Act, 30 CFR 745.13, or other applicable laws or regulations. Thus, this provision is consistent with the Federal lands program which adopted the Alabama State Program as substantive Federal law on all Federal lands in Alabama and made it enforceable by the State and the United States. The reference to the Alabama State Program is intended to encompass the State's Program as approved on July 5, 1984 (49 FR 27500), and any amendments thereto which are approved in accordance with 30 CFR 732.17. Excluded from the scope of the agreement are the authorities and responsibilities reserved to the Secretary pursuant to the Act and 30 CFR 745.13.

Article V: General Requirements

Article V would mutually bind the Governor and the Secretary to the provisions of the cooperative agreement and the conditions and requirements contained in Article V.

Paragraph A of Article V would require that the Alabama Surface Mining Commission (The agency designated by the Governor to administer the agreement) continue to have authority under State law to carry out this cooperative agreement.

Paragraph B of Article V would provide that, upon application for funds, the State may be reimbursed pursuant to section 705(c) of the Act if the cooperative agreement has been implemented and if necessary funds have been appropriated to OSM by Congress. Section 705(c) of the Act provides that a State with a cooperative agreement may receive an increase in its annual grant for the development, administration and enforcement of a State program on Federal lands by an amount which the Secretary determines is approximately equal to the amount the Federal government would otherwise have expended to regulate surface coal mining and reclamation operations on Federal lands within the State. See 30 U.S.C. 1285(c). The reference in section 705(c) to section 523(d) is obviously a typographical error; the correct reference is section 523(c).

The regulations implementing section 705(c) appear at 30 CFR 735.16 through 735.26. If, when reguested by the State, adequate funds have not been appropriated, OSM and the Alabama Surface Mining Commission would meet to decide on appropriate measures to ensure that mining operations are regulated in accordance with the approved State Program. Either party may terminate the cooperative agreement if agreement cannot be achieved. Any funds granted to the State pursuant to the cooperative agreement would be reduced by the amount of any fees collected by the State that are attributable to the Federal lands covered by the agreement, in accordance with Office of Management and Budget (OMB) Circular A–102 (Uniform Requirements for Assistance to State and Local Governments), Attachment E (Program income).

Paragraph C of Article V would require the State to make annual reports to OSM with respect to compliance with this agreement. Paragraph C also provides for a general exchange of information developed under the agreement, unless such an exchange is prohibited by Federal law. Final evaluation reports prepared by OSM on State administration and enforcement of this agreement will be provided to ASMC.

Paragraph D of Article V would require ASMC to maintain the necessary personnel to fully implement this agreement.

Paragraph E of Article V would require that ASMC avail itself of the facilities necessary to carry out the requirements of the agreement. This provision would ensure that the State has access to and utilizes any resources necessary to conduct inspections, investigations, studies, tests, and analyses required to fulfill the requirements of this agreement.

Paragraph F of Article V concerns permit application fees. Fees would be determined according to Section 15 of the Alabama Surface Mining Control and Reclamation Act of 1981, Section 880–X–8B–.07 of the State regulations, and the State Program or Federal law. The State would retain all permit application fees and civil penalties from operations on Federal lands and deposit them in the Alabama Surface Mining Fund. The State would report the amount of these fees in the financial status report required under 30 CFR 735.26. State funding (under paragraph B of Article V) would be reduced by the amount collected from mining on Federal lands.

Article VI: Reveiw of Permit Application Package

Paragraphs A through C of Article VI would describe the procedures the State would follow in the review and analysis of permit application packages (PAP) on Federal lands. "Permit application package" is a term adopted by OSM in revising the Federal lands program (48 FR 6912; February 16, 1983). It appropriately describes the material submitted by an applicant proposing to mine on Federal lands and includes materials submitted with applications for permit revision and renewals.

OSM adopted the term because there are requirements for mining on Federal lands in addition to those required by a permit application under the approved State Program for non-Federal lands. For example, operations on Federal lands may be subject to requirements of the Federal land management agency under Federal laws other than the Act. The package concept allows such information to be included with the permit application required by the approved State Program. See the definition of "permit application package" under 30 CFR 740.5.

The proposed cooperative agreement identifies ASMC as having the primary responsibility for the analysis, review, and approval or disapproval of the permit application package on Federal lands in Alabama. In assuming primary responsibility for review, analysis, and approval or disapproval of permit applications, ASMC would also be responsible for coordinating the review of a permit application package with Federal agencies other than OSM affected by the proposed surface coal mining and reclamation operations to ensure compliance with Federal laws other than the Act and regulations other than those implementing SMCRA. If requested by the State, OSM would assist in identifying Federal agencies which may be affected by the proposed mining operation. Under Paragraph A, an operator on Federal lands would be required by ASMC and the Secretary to submit a permit application package in an appropriate number of copies to ASMC. ASMC would provide a copy to OSM if the PAP involves mining of Federal coal.

At a minimum, the permit application package must include the information necessary for ASMC to make a determination of compliance with the approved State Program and for the Secretary to make determinations of compliance with applicable requirements of other Federal laws and regulations for which he is responsible.

Paragraph B.1. would assign to ASMC the primary responsibility for analysis, review, and approval or disapproval of the PAP. ASMC would also be the principal contact for the applicant on issues concerned with the development, review and approval of the permit application package or application for permit revision or renewal for mining on Federal lands in Alabama, and would be responsible for informing applicants of determinations.

Under Paragraph B.2., ASMC would send a copy of the PAP to the Federal land management agency with a request for review and would be responsible for obtaining the views of other Federal agencies that would be affected by a PAP. ASMC would also forward information to OSM to assist OSM in determining whether the proposed mining operation were limited or prohibited under 522(e) of the Federal Act.

Under Paragraph B.3., ASMC would receive, upon request, assistance from OSM. OSM would be responsible for forwarding information from applicants to ASMC. Any information in ASMC files concerning mines on Federal lands would be available to OSM.

Paragraph B.4. would require ASMC to review the PAP for compliance with the Program.

Paragraph B.5. would require ASMC to include in permits any terms or conditions imposed by the Federal land management agency. ASMC would give written notification to the Federal land management agency, the applicant, and OSM of decisions and findings on the PAP.

Article VI.C. discusses review procedures where Federally-owned coal is involved and, consequently, where the Secretary must approve a mining plan. Under propsoed paragraph C.1., ASMC would have lead responsibility for analysis and review of the permit application part of the PAP for mining such coal. The Department would retain those responsibilities that cannot be delegated to the State, including those under the Mineral Leasing Act (MLA) and the National Environmental Policy Act (NEPA). Working agreements between OSM and ASMC would specify those responsibilities that ASMC would assume. As part of his responsibilities in approving the mining plan under the Mineral Leasing Act, the Secretary would review the operation and reclamation plan component of the permit application to ensure that it complies with the Surface Mining Act.

Paragraph C.2. would designate ASMC as the primary liaison for operators in matters regarding the PAP. As such, ASMC would inform the applicant of all joint State-Federal determinations. ASMC would provide OSM with any information affecting decisions on mining plans, and OSM would provide ASMC with information affecting decisions on PAPs. OSM would not ordinarily contact the applicant regarding the PAP, although there would be no prohibition against doing so.

Under paragraph C.3., the responsibilities of OSM and ASMC would be as follows:

1. ASMC would take on the responsibilities in 30 CFR 740.4(c) (1), (2), (4), (5), and (6).

2. OSM would retain the responsibilities in 30 CFR 740(c) (3) and (7).

3. OSM would assist the State by coordinating the review of the PAP between those Federal agencies involved. OSM would request that the involved Federal agencies submit their findings to OSM within 45 days of receiving the PAP. OSM would then provide ASMC with these findings.

4. OSM would further assist the State by responding to conflicts of the involved Federal agencies and by helping to schedule meetings between the agencies and the State.

5. OSM would exercise its responsibilities in a timely manner and would provide ASMC with a work product within 45 days of receiving the State's request for assistance in reviewing the permit application.

6. OSM would be solely responsible for Federal lease protection bond requirements.

Paragraph C.4. would describe the procedures that OSM and the State would follow in reviewing the PAP. OSM and ASMC would coordinate their activities and exchange information during the review process. The State would review the PAP to ensure compliance with the Program, while OSM would review the PAP to ensure compliance with other Federal laws and regulations. OSM and the State would plan and schedule PAP review and each would choose a project leader, with the OSM project leader designated as the primary point of contact for both during the review process. OSM would provide the State with its initial findings within 50 days of receiving the PAP.

The State would provide OSM with its technical analysis of the PAP and its finding that the PAP complies with the Program. ASMC could then issue the permit before Secretarial approval. However, ASMC would have to advise the operator that the operator could not disturb Federal lands before the mining plan had been approved by the Secretary.

Paragraph C.5. would assign to ASMC sole authority to approve permit revisions not constituting modifications of a mining plan. ASMC would consult with OSM on whether any permit revisions constitute mining plan modifications. OSM may develop guidelines to determine which permit revisions are definitely not mining plan modifications.

Article VII: Inspections

Article VII would specify that ASMC must conduct inspections on Federal lands covered by this agreement and prepare and file State inspection reports in accordance with its approved Program.

Article VII.C. would designate ASMC as the point of contact and primary inspection authority in dealing with the operator. However, the Department would retain the right to conduct inspections of surface coal mining and reclamation operations on Federal lands without prior notice to ASMC for the purpose of evaluating the manner in which the cooperative agreement is being carried out and ensuring that performance and reclamation standards are being met. OSM would ordinarily give ASMC reasonable notice before conducting an inspection so that State inspectors could join in the inspection. Under extraordinary circumstances, such as the threat of imminent harm to the public or the environment, OSM would notify ASMC at least 24 hours prior to a Federal inspection, unless this proves impractical.

This article would preserve OSM's obligation and authority to conduct inspections pursuant to 30 CFR Parts 842 and 843. The right of Federal and State agencies to conduct inspections for purposes outside the scope of the proposed cooperative agreement would not be affected.

Article VIII: Enforcement

Article VIII would set forth the enforcement obligations and authorities of OSM and ASMC.

Under paragraph A, ASMC would have primary enforcement authority on Federal lands in accordance with the requirements of the cooperative agreement and the approved State Program.

Under paragraph B, ASMC would have primary responsibility for enforcement during joint inspections with OSM. Paragraph B would also include a requirement that ASMC notify OSM prior to suspending or revoking a permit.

Paragraph C would preserve OSM's authority to take enforcement action to comply with 30 CFR Parts 843 and 845 where OSM conducted an inspection or where, during a joint inspection with ASMC, the two could not agree on the appropriateness of a particular enforcement action. Such action would be based upon the Act or the substantive provisions contained in the approved State Program, but would use the Federal procedures and penalty system.

Paragraph D would provide that OSM and ASMC notify each other of all violations of applicable regulations and all actions taken on the violations. Paragraph E would provide that personnel of the State and the Department be mutually available to serve as witnesses in enforcement actions taken by either party. Finally, paragraph F would specify that this agreement would not limit the Department's authority to enforce Federal laws other than the Act.

Article IX: Bonds

Under paragraph A, ASMC and the Secretary would require each operator on Federal lands in Alabama to submit a single performance bond payable to both the State and the United States. All applicable State and Federal

requirements would be fulfilled prior to releasing an operator from any obligation covered by the performance bond. If the cooperative agreement is terminated, paragraph A would require that the bond revert to being payable solely to the United States to the extent that Federal lands are involved in the permit area. ASMC would advise OSM of annual adjustments to the bond and release a bond only after OSM concurrence. Departmental concurrence would include coordination with other Federal agencies having jurisdiction over the lands involved.

Article IX.C. would clarify that the performance bond does not meet the requirement for a Federal lease bond under 43 CFR Part 3474, or for the lessee protection bond required in certain circumstances by section 715 of the Act.

Article X: Designating Land Areas Unsuitable for All or Certain Types of Surface Coal Mining Operations

Article X would assign to ASMC authority to designate State and private lands as unsuitable for surface coal mining, while reserving to the Secretary such authority over Federal lands. ASMC and OSM would each notify the other of any petition to designate lands as unsuitable, exchange information when either agency receives a petition that could impact surrounding Federal and non-Federal lands, and solicit and consider each other's views on a petition.

Article XI: Termination of Cooperative Agreement

Article XI would specify that this cooperative agreement may be terminated as specified under 30 CFR 745.15.

Article XII: Reinstatement of Cooperative Agreement

Article XIII would provide that, if terminated, the cooperative agreement may be reinstated under 30 CFR 745.16. That provision allows for reinstatement of the cooperative agreement upon application by the State after remedying the defects for which agreement was terminated and the submission of evidence to the Secretary that the State can and will comply with all of the provisions of the agreement.

Article XIII: Amendment of Cooperative Agreement

Article XIII would provide that the cooperative agreement may be amended by mutual agreement of the Governor and Secretary in accordance with 30 CFR 745.14.

Article XIV: Changes in State or Federal Standards

Paragraph A of Article XIV would recognize that the Secretary or the State may, from time to time, promulgate new or revised performance or reclamation requirements, or enforcement and administration procedures. OSM and ASMC would immediately inform each other of these changes. If it were determined to be necessary to keep the Agreement in force, the State would request necessary legislative action and either the State or OSM would change or revise its regulations or promulgate new regulations, as applicable. Such changes would be made in accordance with 30 CFR Part 732 for changes to the approved State Program and section 501 of the Act for changes to the permanent regulatory program or to the Federal lands program.

Paragraph B would require the State and OSM to provide each other with copies of changes in their respective laws and regulations.

Article XV: Changes in Personnel and Organization

Article XV would require the State and the Department to advise each other of substantial changes in organization, funding, staff, or other changes which could affect administration or enforcement of the cooperative agreement.

Article XVI: Reservation of Rights

Article XVI would recognize that the Act, 30 CFR 745.13, and other authorities prohibit the Secretary from delegating certain authorities to the State. Article XVI would state that this agreement does not delegate nor shall it be construed to delegate any authority that the Secretary has under 30 CFR 745.12, or under laws other than the Act, including those listed in Appendix A of this cooperative agreement.

IV. Procedural Matters

1. E.O. 12291 and Regulatory Flexibility Act

In a "Determination of Significance" document prepared on December 31, 1979, and approved by the Assistant Secretary, Energy and Minerals, on January 7, 1980, the Department determined that the "promulgation of proposed or final rules for entering into a cooperative agreement with a State pursuant to 30 U.S.C. 1273 for State regulation of surface coal mining and reclamation operations on Federal lands was not a significant action and would not require a regulatory analysis." A copy of this determination was filed with the Department's Office of Policy Analysis and the Division of General Law in accordance with Departmental procedures.

The Department has reviewed this determination in light of Executive Order 12291, February 17, 1981; the Regulatory Flexibility Act (Pub. L. 96–354); and the Paperwork Reduction Act of 1980 (Pub. L. 96–511). Having conducted this review, the Department has determined that this document is not a major rule and does not require a regulatory impact analysis under Executive Order 12291. The document will not have a significant economic effect on a substantial number of small entities and therefore does not require a regulatory flexibility analysis under the Regulatory Flexibility Act, 5 U.S.C. 605(b). This determination was made by the Director, OSM and approved by the Assistant Secretary, Energy and Minerals. A copy is on file in the OSM Administrative Record Room, room 5315, 1100 L Street NW., Washington, D.C. 20005.

2. Recordkeeping and Reporting Requirements

There are recordkeeping and reporting requirements in the proposed rules which are the same as and required by the permanent program regulations. Those regulations received clearance from the Office of Management and Budget under 44 U.S.C. 3507 and were assigned the following clearance numbers:

Location of requirement	OMB clearance No.
Article VI.A (Required by CFR Part 786)	1029–0041
Article VI.A (Required by CFR Part 840)	1029–0051
Article VI.A (Required by CFR Part 800)	1029–0043

3. National Environmental Policy Act

Proceedings relating to adoption of a permanent program cooperative agreement are part of the Secretary's implementation of the Federal lands program pursuant to section 523 of the Act. Such proceedings are, therefore, exempt under section 702(d) of the Act from the requirements to prepare a detailed statement pursuant to section 102(2)(C) of the National Environmental Policy Act of 1969 (42 U.S.C. 4332(2)(C)).

List of Subjects in 30 CFR Part 901

Coal mining, Intergovernmental relations, Surface mining, Underground mining.

Dated January 16, 1985.

Brant W. Blauch,

Acting Director, Office of Surface Mining.

(Pub. L. 95–87, Surface Mining Control and Reclamation Act of 1977 (30 U.S.C. 1202 *et seq.*))

For the reasons set forth herein, it is proposed to amend 30 CFR Part 901 as follows:

PART 901—ALABAMA

1. Section 901.30 is added to read as follows:

§ 901.30 State-Federal Cooperative Agreement.

Cooperative Agreement

The Governor of the State of Alabama and the Secretary of the Department of the Interior enter into a Cooperative Agreement (Agreement) to read as follows:

Article I: Introduction, Purpose and Responsible Agencies

A. *Authority:* This Agreement is authorized by section 423(c) of the Surface Mining Control and Reclamation Act (Federal Act), 30 U.S.C. 1273(c), which allows a State with a permanent regulatory program approved by the Secretary under 30 U.S.C. 1253, to elect to enter into an Agreement for State regulation of surface coal mining and reclamation operations on Federal lands. This Agreement provides for State regulation of surface coal mining and reclamation operations on Federal lands in Alabama, consistent with State and Federal Acts governing such activities, the Federal lands program (30 CFR Parts 740–746) and the Alabama State Program (Program).

B. *Purpose:* The purposes of this Agreement are to (a) foster Federal-State cooperation in the regulation of surface coal mining and reclamation operations; (b) eliminate intergovernmental overlap and duplication; and (c) provide unifrom and effective application of the Program on all lands in Alabama in accordance with the Act, the Program, and this Agreement.

C. *Responsible Administrative Agencies:* The Alabama Surface Mining Commission (ASMC) shall be responsible for administering this Agreement on behalf of the Governor on Federal lands throughout Alabama. The Office of Surface Mining (OSM) shall administer this Agreement on behalf of the Secretary.

Article II: Effective Date

After being signed by the Secretary and the Governor, this Agreement shall take effect 30 days after publication in the **Federal Register** as a final rule. This Agreement shall remain in effect until terminated as provided in Article XI.

Article III: Definitions

The terms and phrases used in this Agreement which are defined in the Federal Act, 30 CFR Parts 700, 701, and 740, the approved State Program and the State Act, and the rules and regulations promulgated pursuant ot those Acts, shall be given the meanings set forth in said definitions. Where there is a conflict between the above referenced State and Federal definitions, the definition used in the approved State Program shall apply, except in the case of a term which defines the Secretary's continuing responsibilities under the Federal Act or other laws.

Article IV: Applicability

In accordance with the Federal lands program in 30 CFR Part 745, the laws, regulations, terms and conditions of the Program are applicable to Federal lands in Alabama except as otherwise stated in this Agreement, the Federal Act, 30 CFR 745.13, or other applicable laws or regulations.

Article V: General Requirements

The Governor and the Secretary affirm that they will comply with all of the provisions of this Agreement.

A. *Authority of State Agency:* ASMC has and shall continue to have the authority under State law to carry out this Agreement.

B. *Funds:* 1. Upon application by ASMC and subject to appropriations, OSM shall provide the State with the funds to defray the costs associated with carrying out its responsibilities under this Agreement as provided in section 705(c) of the Federal Act and 30 CFR 735.16. Such funds shall cover the full cost incurred by ASMC in carrying out these responsibilities, provided that such cost does not exceed the estimated cost the Federal government would have expended on such responsibilities in the absence of this Agreement; and provided that such State-incurred cost per permitted acre of Federal lands does not exceed the per permitted acre costs for administration and enforcement of the State's program on non-Federal and non-Indian lands during the same time period.

2. The ratio of Federal to non-Federal lands shall be calculated by listing each mine anticipated to be under permit any time during the grant period and indicating the number of acres, by mine, that is Federal and non-Federal. This information will be provided to OSM's Birmingham Field Office in tabular form with each mine identified. ASMC will also provide a detailed explanation of its method and calculations used to estimate overall costs. OSM's Birmingham Field Office, in conjunction with OSM's Eastern Technical Service Center, will estimate the amount the Federal Government would have expended for regulation on Federal lands in Alabama in the absence of this Agreement.

3. As necessary, OSM and the State will discuss the OSM Federal lands cost estimate, the ASMC-prepared list of acres by mine and the State's overall cost estimate. After resolution of any issues, ASMC will submit its grant application to OSM's Birmingham Field Office. Acreage calculations agreed to by OSM will be used as the basis for reconciling final costs at the end of the grant period. The Federal lands/non-Federal lands ration will be applied to the final eligible total State expenditures to arrive at the total Federal reimbursement due the State.

4. If ASMC applies for a grant but sufficient funds have not been appropriated to OSM, OSM and ASMC shall promptly meet to decide on appropriate measures that will insure that mining operations on Federal lands in Alabama are regulated in accordance with the Program. If agreement cannot be reached, either party may terminate this Agreement in accordance with Article XI.

5. Funds provided to ASMC under this Agreement shall be adjusted in accordance with Office of Management and Budget Circular A–102, Attachment E.

C. *Reports and Records:* ASMC shall make annual reports to OSM containing information with respect to compliance with the terms of this Agreement, pursuant to 30 CFR 745.12(d). ASMC and OSM shall exchange, upon request, except where prohibited by federal law, information developed under this Agreement.

OSM shall provide ASMC with a copy of any final evalaution report prepared concerning State administration and enforcement of this Agreement.

D. *Personnel:* ASMC shall have the necessary personnel to fully implement this Agreement in accordance with the provisions of the Federal Act and the approved State Program.

E. *Equipment and Laboratories:* ASMC shall assure itself access to equipment, laboratories, and facilities with which all inspections, investigations, studies, tests, and analyses can be performed which are necessary to carry out the requirements of this Agreement.

F. *Permit Application Fees and Civil Penalties:* The amount of the fee accompanying an application for a permit for operations on Federal lands in Alabama shall be determined in accordance with Section 15 of the Alabama Surface Mining Control and Reclamation Act of 1981, § 771.25 of the State regulations, and the applicable provisions of the State Program or Federal law. All permit and civil penalty fees collected from operations on Federal lands will be retained by the State and shall be deposited with the State Treasurer in the Alabama Surface Mining Fund. The financial status report submitted pursuant to 30 CFR 735.28 shall include a report of the amount of fees collected during the prior State fiscal year.

Article VI: Review of Permit Application Package

A. *Submission of Permit Application Package:* ASMC and the Secretary shall require an operator proposing to conduct surface coal mining on Federal lands covered by this Agreement to submit a permit application package (PAP) in an appropriate number of copies to ASMC. If the PAP involves mining of Federally-owned coal, ASMC shall furnish OSM a copy. The PAP shall be in the form required by ASMC and include any supplemental information rquired by OSM or the Federal land management agency. At a minimum, the PAP shall include the information necessary to ASMC to make a determination of compliance with the State Program and for the appropriate Federal agency to make a determination of compliance with applicable requirements of

Federal laws and regulations for which they are responsible.

B. *Review Procedures Where Federally-Owned Coal Is Not Involved:* 1. ASMC shall assume primary responsibility for the analysis, review and aproval or disapproval of the permit application component of the PAP required by 30 CFR 740.13 for surface coal mining and reclamation operations on Federal lands in Alabama not containing leased Federal coal. ASMC shall be the primary point of contact for operators regarding decisions on the PAP and will be responsible for informing the applicant of determinations.

2. Upon receipt of a PAP that involves surface coal mining and reclamation operations on Federal lands not containing leased Federal coal, ASMC shall (1) transmit a copy of the complete PAP to the Federal Land Management Agency with a request for review pursuant to 30 CFR 740.13(b) (4), and (2) provide OSM with the relevant information to allow OSM to determine whether the operations are prohibited or limited by the requirements of section 522(e) of the Federal Act (30 U.S.C. 1272(e)) and 30 CFR Parts 760–762 with respect to Federal areas designated by Congress as unsuitable for mining. ASMC shall be responsible for obtaining, in a timely manner, the views and determinations of any other Federal agencies with jurisdiction or responsibility over Federal lands affected by the operations proposed in a PAP in Alabama.

3. OSM will provide technical assistance to ASMC when requested if available resources allow and will process requests for determinations of compatibility and valid existing rights under 30 CFR Part 761 relating to Federal areas designated by Congress as unsuitable for mining. OSM will be responsible for ensuring that any information OSM receives from an applicant is promptly sent to ASMC. OSM shall have access to ASMC files concerning operations on Federal lands. The Secretary reserves the right to act independently of ASMC to carry out his responsibilities under laws other than the Federal Act. A copy of all resulting correspondence with the applicant that may have a bearing on decisions regarding the PAP shall be sent to ASMC.

4. ASMC shall review the PAP for compliance with the Program.

5. The permit issued by ASMC shall incorporate any terms or conditions imposed by the Federal land management agency, including conditions relating to post-mining land use, and shall condition the initiation of surface coal mining and reclamation operations on compliance with the requirements of the Federal land management agency. After making its decision on the PAP, ASMC shall send a notice to the applicant, the Federal land management agency, and OSM, with a copy of the permit and written findings.

C. *Review Procedures Where Federally-Owned Coal is Involved:* 1. ASMC shall assume primary responsibility for the analysis and review of the permit application component of the PAP for surface coal mining and reclamation operations on Federal lands in Alabama where a mining plan is required by 30 CFR 746.11. OSM, as requested, shall assist the State in this analysis and review. The Department shall concurrently carry out its responsibilities under the Mineral Leasing Act, the National Environmental Policy Act (NEPA), and other applicable Federal laws that cannot be delegated to the State. Responsibilities and decisions which can be delegated to the State under other applicable Federal laws may be specified in working agreements between OSM and the State without amendment to this Agreement. The Department shall carry out these responsibilities in accordance with the Federal lands program and this Agreement in a timely manner so as to avoid, to the extent possible, duplication of the responsibilities of the State as set forth in this Agreement and the Program. The Secretary will consider the information in the PAP and, where appropriate, make decisions required by the Federal Act, MLA, NEPA, and other Federal laws.

2. ASMC will be the primary point of contact for operators regarding the review of the PAP, except on matters concerned exclusively with the 43 CFR Part 3480 regulations administered by the Bureau of Land Management (BLM). ASMC will be responsible for informing the applicant of all joint State-Federal determinations. The Department may act independently of ASMC to carry out responsibilities under laws other than the Federal Act or provisions of the Federal Act not covered by the Program, and in instances of disagreement over the Federal Act and the Federal lands program. ASMC shall send to OSM copies of any correspondence with the applicant and any information received from the applicant which may have a bearing on the mining plan. OSM shall send to ASMC copies of all OSM correspondence with the applicant which may have a bearing on the PAP. As a matter of practice, OSM will not independently initiate contacts with applicants regarding completeness or deficiencies of the PAP with respect to matters covered by the Program.

3. ASMC shall assume the responsibilities listed in 30 CFR 740.4(c) (1), (2), (4), (5) and (6). OSM shall retain the responsibilities listed in 30 CFR 740(c) (3) and (7). OSM shall assist ASMC in carrying out ASMC's responsibilities by:

(a) Distributing copies of the PAP to, and coordinating the review of the PAP among, all Federal agencies which have responsibilities relating to decisions on the package. This shall be done in a manner which ensures timely identification, communication and resolution of issues relating to those Federal agencies' statutory requirements. OSM shall request that such other Federal agencies furnish their findings and any requests for additional data to OSM within 45 calendar days of receipt of the PAP.

(b) Providing ASMC with the analyses and conclusions of other Federal agencies.

(c) Addressing conflicts and difficulties of the other Federal agencies in a timely manner.

(d) Assisting in scheduling joint meetings as necessary between State and Federal agencies.

(e) Where OSM is assisting ASMC in reviewing the permit application, furnishing to ASMC the work product within 45 calendar days of receipt of the State's request for such assistance, or earlier if mutually agreed upon by OSM and ASMC.

(f) Exercising its responsibilities in a timely manner as set forth in a mutually agreed upon schedule, governed to the extent possible by the deadlines established in the Program.

(g) Assuming all responsibility for ensuring compliance with any Federal lessee protection bond requirement.

4. Review of the PAP:

(a) OSM and ASMC shall coordinate with each other during the review process as needed. ASMC shall keep OSM informed of findings during the review process which bear on the responsibilities of OSM or other Federal agencies. OSM shall ensure that any information OSM receives which has a bearing on decisions regarding the PAP is promptly sent to ASMC.

(b) ASMC shall review the PAP for compliance with the Program.

(c) OSM shall review the PAP for compliance with the requirements of other Federal laws and regulations. OSM and ASMC shall develop a work plan and schedule for PAP review and each shall identify a person as the project leader. The OSM project leader shall serve as the primary point of contact between OSM and ASMC throughout the review process. Not later than 30 days after receipt of the PAP, OSM shall furnish ASMC with its preliminary findings on the PAP and specify any requirements for additional data. To the extent practicable, ASMC shall provide OSM all available information that may aid OSM in preparing any findings.

(d) ASMC shall provide to OSM written findings indicating that the PAP is in compliance with the Program, and a technical analysis of the PAP.

(e) ASMC may proceed to issue the permit in accordance with the Program prior to the necessary Secretarial decision on the mining plan, provided that ASMC advises the operator in the permit that Secretarial approval of the mining plan must be obtained before the operator may directly affect Federal lands. ASMC shall reserve the right to amend or rescind any requirements of the approved permit to conform with any terms or conditions imposed by the Secretary in his approval of the mining plan.

5. Prior to acting on a permit revision or renewal, ASMC shall consult with OSM on whether such revision or renewal constitutes a mining plan modifications under 30 CFR 746.18. OSM shall inform ASMC within 30 days of receiving notice of a proposed revision or renewal, whether the permit revision or renewal constitutes a mining plan modification. Permit revision or renewals which do not constitute mining plan modification shall be appoved solely by the State.

OSM may establish criteria consistent with 30 CFR 746.18 to determine which permit revisions and renewals clearly do not constitute mining plan modifications. Such revisions or renewals may be approved by ASMC before it submits copies of the revision or renewal to OSM.

Article VII: Inspections

A. ASMC shall conduct inspections on Federal lands and prepare and file inspection reports in accordance with the Program.

B. ASMC shall, subsequnt to conducting any inspection, and on a timely basis, file with OSM a legible copy of the completed State inspection report.

C. ASMC will be the point of contact and primary inspection authority in dealing with the operator concerning operations and compliance with the requirements covered by this Agreement, except as described hereinafter. Nothing in this Agreement shall prevent inspections by authorized Federal or State agencies for purposes other than those covered by this Agreement. The Department may conduct any inspections necessary to comply with 30 CFR Parts 842 and 843 or its obligations under laws other than the Federal Act.

D. OSM shall ordinarily give ASMC reasonable notice of its intent to conduct an inspection under 30 CFR 842.11 in order to provide State inspectors an opportunity to join in the inspection. When OSM is responding to a citizen complaint of an imminent danger to the public health and safety, or of significant, imminent environmental harm to land, air or water resources, pursuant to 30 CFR 842.11(b)(1)(ii)(C), it will contact ASMC no less than 24 hours prior to the Federal inspection, if practicable, to facilitate a joint Federal/State inspection. All citizen complaints which do not involve an imminent danger shall be referred to ASMC for action. The Secretary reserves the right to conduct inspections without prior notice to ASMC to carry out his responsibilities under the Federal Act.

Article VIII: Enforcement

A. ASMC shall have primary enforcement authority under the Federal Act concerning compliance by operators with the requirements of this Agreement and the Program. Enforcement authority given to the Secretary under other laws and orders, including but not limited to those listed in Appendix A, is reserved to the Secretary.

B. During any joint inspection by OSM and ASMC shall have primary responsibility for enforcement procedures, including issuance of orders of cessation, notices of violation, and assessment of penalties. The ASMC shall inform OSM prior to issuance of any decision to suspend or revoke a permit.

C. During any inspection made solely by OSM or any joint inspection where the ASMC and OSM fail to agree regarding the propriety of any particular enforcement action, OSM may take any enforcement action necessary to comply with 30 CFR Parts 843 and 845. Such enforcement action shall be based on the performance standards included in the regulations of the approved Program, and shall be taken using the procedures and penalty system contained in 30 CFR Parts 843 and 845.

D. ASMC and the Department shall promptly notify each other of all violations of applicable laws, regulations, orders, or approved mining permits subject to this Agreement, and of all actions taken with respect to such violations.

E. Personnel of ASMC and representatives of the Department shall be mutually available to serve as witnesses in enforcement actions taken by either party.

F. This Agreement does not limit the Department's authority to enforce violations of Federal law which establish standards and requirements which are authorized by laws other than the Federal Act.

Article IX: Bonds

A. ASMC and the Secretary shall require each operator on Federal lands to submit a single performance bond payable to Alabama and the United States to cover the operator's responsibilities under the Federal Act and the Program. Such performance bond shall be conditioned upon compliance with all requirements of the Federal Act, the Program and any other requirements imposed by the Department under the MLA, as amended. Such bond shall provide that if the Agreement is terminated, the bonds shall be payable only to the United States to the extent that Federal lands are involved.

B. Prior to releasing the operator from any obligation under such bond, the ASMC shall obtain the concurrence of OSM. The ASMC shall also advise OSM of annual adjustment to the performance bond, pursuant to the Program. Departmental concurrence shall include coordinate with other Federal agencies having authority over the lands involved.

Such bond shall be subject to forfeiture with the consent of OSM, in accordance with the procedures and requirements of the Program.

C. Submission of a performance bond does not satisfy the requirement for a Federal lease bond required by 30 CFR Subpart 3474 or for a lessee protection bond required in addition to a performance bond, in certain circumstances, by section 715 of the Federal Act.

Article X: Designating Land Areas Unsuitable for All or Certain Types of Surface Coal Mining Operations

A. When either ASMC or OSM receives a petition that could impact adjacent Federal and non-Federal lands, the agency receiving the petition shall (1) notify the other of receipt and the anticipated schedule for reaching a decision; and (2) request and fully consider data, information and views of the other.

B. Authority to designate State and private lands as unsuitable for mining is reserved to the State. Authority to designate Federal lands as unsuitable for mining is reserved to the Secretary.

Article XI: Termination of Cooperative Agreement

This Agreement may be terminated by the Governor or the Secretary under the provisions of 30 CFR 745.15.

Article XII: Reinstatement of Cooperative Agreement

If this Agreement has been terminated in whole or in part it may be reinstated under the provisions of 30 CFR 745.16.

Article XIII: Amendment of Cooperative Agreement

This Agreement may be amended by mutual agreement of the Governor and the Secretary in accordance with 30 CFR 745.14.

Article XIV: Changes in State or Federal Standards

A. The Department or the State may from time to time promulgate new or revised performance or reclamation requirements or enforcement and administration procedures. Each party shall, if it determines it to be necessary to keep this Agreement in force, change or revise its regulations or request necessary legislative action. Such changes shall be made under the procedures of 30 CFR Part 732 for changes to the State Program and under the procedures of section 501 of the Federal Act for changes to the Federal lands program.

B. ASMC and the Department shall provide each other with copies of any changes to their respective laws, rules, regulations or standards pertaining to the enforcement and administration of this Agreement.

Article XV: Changes in Personnel and Organization

Each party to this Agreement shall notify the other, when necessary, of any changes in personnel, organization and funding, or other changes that would affect the implementation of this Agreement to ensure coordination of responsibilities and facilitate cooperation.

Article XVI: Reservation of Rights

In accordance with 30 CFR 745.13, this Agreement shall not be construed as waiving or preventing the assertion of any rights that have not been expressly addressed in ths Agreement that the State or Secretary may have under other laws or regulations, including but not limited to those listed in Appendix A.

Dated:_____
Signed:_____

Governor of Alabama.

Dated:_____
Signed:_____

Secretary of the Interior.

Appendix A

1. The Federal Land Policy and Management Act, 43 U.S.C. 1701 *et seq.*, and implementing regulations.

2. The Mineral Leasing Act of 1920, 30 U.S.C. 181 *et seq.*, and implementing regulations including 43 CFR Part 3480.

3. The National Environmental Policy Act of 1969, 42 U.S.C. 4321 *et seq.*, and implementing regulations including 40 CFR Part 1500.

4. The Endangered Species Act, 16 U.S.C. 1531 *et seq.*, and implementing regulations including 50 CFR Part 402.

5. The National Historic Preservation Act of 1966, 16 U.S.C. 470 *et seq.*, and implementing regulations, including 36 CFR Part 800.

6. The Clean Air Act, 42 U.S.C. 7401 *et seq.*, and implementing regulations.

7. The Federal Water Pollution Control Act, 33 U.S.C. 1251 *et seq.*, and implementing regulations.

8. The Resource Conservation and Recovery Act of 1976, 42 U.S.C. 6901 *et seq.*, and implementing regulations.

9. The Reservoir Salvage Act of 1960, amended by the Preservation of Historical and Archaeological Data Act of 1974, 16 U.S.C. 469 *et seq.*

10. Executive Order 1593 (May 13, 1971), Cultural Resource Inventories on Federal Lands.

11. Executive Order 11988 (May 24, 1977), for flood plain protection. Executive Order 11990 (May 24, 1977), for wetlands protection.

12. The Mineral Leasing Act for Acquired Lands, 30 U.S.C. 351 *et seq.*, and implementing regulations.

13. The Stock Raising Homestead Act of 1916, 43 U.S.C. 291 *et seq.*

14. The Constitution of the United States.

15. The Constitution of the State and State Law.

[FR Doc. 85-1694 Filed 1-22-85; 8:45 am]

BILLING CODE 4310-05-M

30 CFR Part 917

Consideration of Amendments to the Kentucky Program Under the Surface Mining Control and Reclamation Act of 1977

AGENCY: Office of Surface Mining Reclamation and Enforcement (OSM), Interior.

ACTION: Reopening of public comment period.

SUMMARY: OSM is reopening the period for review and comment on certain amendments submitted by the Commonwealth of Kentucky to its program for the regulation of surface coal mining and reclamation in the State. The amendments relate to Kentucky's revised regulations pertaining to contemporaneous reclamation deferments with respect to condition (m) and cancellation of surety bonds.

DATE: Written comments, data or other relevant information must be received on or before 4:00 p.m. February 7, 1985 to be considered. Comments submitted after this date may not necessarily be considered.

ADDRESS: Comments should be sent or hand-delivered to: W.H. Tipton, Director, Lexington Field Office, Office of Surface Mining, 340 Legion Drive, Suite 28, Lexington, Kentucky 40504.

FOR FURTHER INFORMATION CONTACT: W.H. Tipton, Director, Lexington Field Office, Office of Surface Mining, 340 Legion Drive, Lexington, Kentucky 40504; Telephone: (606) 233-7327.

SUPPLEMENTARY INFORMATION: By a letter dated August 3, 1984, OSM received, pursuant to the 30 CFR 732.17 State program amendment procedures, revised regulations amending the Kentucky program. On August 31, 1984, OSM published a notice in the **Federal Register** (49 FR 34529) announcing receipt of the amendments to the Kentucky progam and inviting public comment thereon. The public comment period closed October 1, 1984. A public hearing was not scheduled because no one expressed a desire to testify. However, one party expressed an interest in a public meeting, which was held on September 25, 1984, following public notice. A summary of the meeting can be found in the Administrative Record, Document No. KY 603.

On October 15, 1984, OSM received additional material from Kentucky pertaining to reclamation deferments and cancellation of surety bonds. This material consists of further revisions to the Kentucky Administrative Regulations (KAR) at 405 KAR 10:035 and 405 KAR 16:020. One change to 405 KAR 10:035 establishes the effective date of the notice of intent to cancel a surety bond as the date of service or seven days after mailing the notice by certified mail to all known addresses, whichever comes first. Another change permits an attorney-in-fact of the surety company to sign the notice of intent to cancel. The additional revision to Section 5(5)(b) of 405 KAR 16:020 provides a minor technical clarification of the cabinet's reclamation deferment enforcement and revocation procedures.

OSM is reopening the comment period for an additional 15 days to allow the public sufficient time to review and comment on the above Kentucky amendments. Written comments should be specific, pertain only to the issues proposed in this rulemaking and include explanations of why the commenter believes or does not believe that the proposed amendments are in accordance with SMCRA and no less effective than its implementing regulations. Pursuant to 30 CFR 732.17(h)(2)(ii), each requestor may receive, free of charge, one single copy of the proposed amendment by contacting OSM's Lexington Field Office listed under **ADDRESS.**

This announcement is made in keeping with OSM's commitment to public participation as a vital component in fulfilling the purposes of SMCRA.

List of Subjects in 30 CFR Part 917

Coal mining, Intergovernmental relations, Surface mining, Underground mining.

Dated: January 16, 1985.

(Pub. L. 95-87, Surface Mining Control and Reclamation Act of 1977 (30 U.S.C. 1201 *et seq.*))

William B. Schmidt,

Assistant Director, Program Operations and Inspection.

[FR Doc. 85-1730 Filed 1-22-85; 8:45 am]

BILLING CODE 4310-05-M

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 123

[OW-3-FRL-2761-1]

Revision of West Virginia's NPDES Program Transferring Authority Over Coal Mines and Coal Preparation Plants From the West Virginia Department of Natural Resources; Division of Water Resources to Its Division of Reclamation

AGENCY: Environmental Protection Agency.

ACTION: Notice of proposed rulemaking.

SUMMARY: This proposed rule will approve the transfer of certain water pollution related regulatory authorities and responsibilities under the Clean Water Act, 33 U.S.C. 1251 et seq., from one Division of a West Virginia State Agency to another without any siginficant change in the substance of those State regulatory authorities or responsibilities. Currently the West Virginia Department of Natural Resources ("DNR"), Division of Water Resources ("DWR") administers the National Pollutant Discharge Elimination System ("NPDES") permit program for regulating all discharges of pollutants to the waters of the State pursuant to section 402 of the Clean Water Act, 33 U.S.C. 1342. This proposed rule will approve transfer of these NPDES authorities for regulation of discharges from coal mines and coal preparation plants (and all refuse and waste therefrom) from the Division of Water Resources to the Division of Reclamation ("DR"), still within the Department of Natural Resources. The DR is already charged with other regulatory authority, including permitting authority, over these facilities, and administration of both programs by the same regulatory authority will result in increased efficiencies for both the regulatory authority and the regulated public.

DATE: Comments must be submitted on or before February 22, 1985.

ADDRESS: All comments regarding the proposed rulemaking submitted on or

before 30 days after publication of this notice will be considered by EPA and should be directed to: Alvin R. Morris (3WM00) Director, Water Management Division, U.S. EPA Region III, 6th and Walnut Sts., Philadelphia, Pa. 19106.

FOR FURTHER INFORMATION CONTACT: Jed Z. Gallen, Esq. (3RC30), at (215) 597–9882, Office of Regional Counsel, U.S. EPA Region III, 6th and Walnut Sts., Philadelphia, Pa. 19106.

SUPPLEMENTARY INFORMATION: On May 10, 1982, the State of West Virginia was given approval by EPA to administer, through its Division of Water Resources, the NPDES permit program for regulating discharges of pollutants to waters within its boundaries. The State has also received approval from the Department of Interior to administer the Surface Mining Control and Reclamation Act of 1977 ("SMCRA"), regulating the coal mining industry. This broad regulatory program is administered in West Virginia by the Department of Natural Resources' Division of Reclamation ("DR").

As applied to coal mining and coal preparation plants, the reguirements of the NPDES and SMCRA permit programs are overlaping and duplicative. To minimize confusion and inefficent duplication of effort, as well as to provide the coal industry with a one-stop permitting process, West Virginia has requested pursuant to 40 CFR 123.62, that EPA approve a modification of its NPDES program to permit the Division of Reclamation to assume all NPDES responsibilities with respect to coal mines and preparation plants that are currently performed by the Division of Water Resources.

In order to accomplish this shift of regulatory authority, the West Virginia Legislature enacted S.B. 745 (codified as W. Va. Code section 20–6–43) during the 1984 session, and the Department of Natural Resources promulgated regulations codified as West Virginia Administrative Regulations, Chapter 20, Article 6, Series VII, Section 10.

Based on the foregoing, it is the tentative decision of the Regional Administrator of EPA Region III to approve the modification of the West Virginia NPDES program authorization to authorize the transfer of authorities as described above from the DWR to the DR. No substative rights or obligations of any person will be altered or affected by this program modification. The final decision to approve, conditionally approve, or disapprove the proposed program modification will be based on the comments received, and on a determination of whether the modification is consistent with the requirements of the Clean Water Act and 40 CFR Part 123. A public hearing on this proposed modification will be held if significant public interest in a hearing is expressed.

This Notice of Proposed Rulemaking is referenced under the Clean Water Act. Pursuant to the provisions of 5 U.S.C. 605(b), I hereby certify that this proposed approval will not have a significant economic impact on a substantial number of small business entities.

Dated: January 5, 1985.

Thomas P. Eichler,

Regional Administrator, EPA Region III.

[FR Doc. 85–1679 Filed 1–22–85; 8:45 am]

BILLING CODE 6560–50–M

FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 73

[BC Docket No. 80–157; RM–3363]

TV Broadcast Station in Santa Barbara, CA; Order Providing Time for Filing Comments and Reply Comments

AGENCY: Federal Communications Commission.

ACTION: Order providing time for comments and reply comments.

SUMMARY: This action reopens BC Docket No. 80–157 involving the proposed assignment of VHF Channel *10 for Santa Barbara, California, for a 30 day comment period and a 15 day reply comment period to allow review of a summary of information collected by the Commission's Office of Science and Technology.

DATE: Comments are due by February 15, 1985 and replies by March 4, 1985.

ADDRESS: Federal Communications Commission, Washington, D.C. 20554.

FOR FURTHER INFORMATION CONTACT: Arthur Scrutchins, Mass Media Bureau, (202) 634–6530.

SUPPLEMENTARY INFORMATION:

List of Subjects in 47 CFR Part 73

Television broadcasting.

Order Providing Time for Comments and Reply Comments

In the matter of amendment of § 73.606(b), Table of Assignments, TV Broadcast Stations, (Santa Barbara, California), BC Docket No. 80–157, RM–3363.

Adopted: January 2, 1985.
Released: January 7, 1985.

By the Chief, Policy and Rules Division.

1. The Commission has before it the *Notice of Proposed Rule Making*, 45 FR 28770, published April 30 1980, proposed the assignment of VHF Channel *10 to Santa Barbara, California, with a reservation for noncommercial educational use, in response to a petition filed by KCPB, Inc. ("KCPB"), permittee of Station KCPB–FM, a noncommercial educational station in Thousand Oaks, California. McGraw-Hill Broadcasting Company, Inc. (McGraw-Hill), licensee of Station KGTV/TV (Channel 10) San Diego, California, filed an opposition.

2. McGraw-Hill opposed the assignment of Channel *10 for Santa Barbara due to the claim of harmful interference along the southern California coast and specifically to the service of Station KGTV in San Diego. In support of its arguments, McGraw-Hill made an extensive technical showing. On December 12, 1980, the Commission requested the assistance of its Office of Science and Technology in evaluating the merits of McGraw-Hill's opposition.

3. At the time of the Commission's request, OST was involved in a long term VHF/UHF measurement program in southern California for determining *inter alia*, the alleged effect of anomalous propagation conditions along the southern California coast. OST now reports that it has completed the initial analysis of the data.

4. Inasmuch as the information collected by OST is pertinent to the instant proceeding, we believe that it would be in the public interest to make a copy of these findings available for review and comment. Therefore, a summary of the information collected by OST will be placed in the official record and we will reopen BC Docket No. 80–157 for a comment and reply comment period on OST's findings.

5. Accordingly, comments must be filed on or before February 15, 1985 and reply comments must be filed on or before March 4, 1985.

Federal Communications Commission.

Charles Schott,

Chief, Policy and Rules Division, Mass Media Bureau.

[FR Doc. 85–1614 Filed 1–22–85; 8:45 am]

BILLING CODE 6712–01–M

DEPARTMENT OF TRANSPORTATION

Federal Highway Administration

49 CFR Parts 390, 391, 392, 393, 394, 395, 396, 397, 398, and 399

[BMCS Docket No. MC-114; Notice No. 85-1]

Federal Motor Carrier Safety Regulations

AGENCY: Federal Highway Administration (FHWA), DOT.

ACTION: Advance notice of proposed rulemaking; closing dockets.

SUMMARY: Section 206 of the Motor Carrier Safety Act of 1984 directs the Department of Transportation to issue regulations, pertaining to commercial motor vehicle safety, within 18 months from October 30, 1984, the date of enactment. The purpose of this notice is to (1) advise the public what areas of the Federal Motor Carrier Safety Regulations (FMCSR) are being considered for revision, rescission, or additions, (2) request comments on those areas under consideration, and (3) to incorporate the above named dockets and the comments into this rulemaking action.

DATE: Comments must be received on or before March 11, 1985.

ADDRESS: All comments should refer to the docket number that appears at the top of this document and must be submitted (preferably in triplicate) to Room 3404, Bureau of Motor Carrier Safety, 400 Seventh Street SW., Washington, D.C. 20590.

FOR FURTHER INFORMATION CONTACT: Mr. Neill L. Thomas, Bureau of Motor Carrier Safety, (202) 426-9767; or Mr. Thomas P. Holian, Office of the Chief Counsel, (202) 426-0346, Federal Highway Administration, Department of Transportation, 400 Seventh Street SW., Washington, D.C. 20590. Office hours are from 7:45 a.m. to 4:15 p.m. et, Monday through Friday.

SUPPLEMENTARY INFORMATION: The following open MC dockets are being incorporated into this rulemaking action, and therefore are being closed:

MC-64—Employee Safety and Health Standards
MC-93—Migratory Workers
MC-98—Exemptions—Operations Involving Retail Fertilizer Distribution to Farms
MC-99-1—Driver's Record of Duty Status
MC-100—Written Examination of Drivers
MC-104—Qualifications of Drivers
MC-109—Reporting of Accidents.

The purposes of the Motor Carrier Safety Act of 1984 (Act), Pub. L. 98-554, 98 Stat. 2829, as stated by the Congress, are to promote the safe operation of commercial motor vehicles, to minimize dangers to the health of operators of commercial motor vehicles and other employees whose employment directly affects motor carrier safety, and to assure increased compliance with traffic laws and with the commercial motor vehicle safety and health rules, regulations, standards, and orders issued pursuant to this Act.

The Congress found that it is in the public interest to enhance commercial motor vehicle safety and to reduce highway fatalities, injuries, and property damage. By having more uniform commercial motor vehicle measures and strengthened enforcement, the number of fatalities and injuries would be reduced and the level of property damage related to commercial motor vehicle operations would also be reduced. Congress also found that it is in the public interest to enhance protection of the health of commercial motor vehicle operators.

Congressional Directive

Section 206 of the Act directs the Secretary to issue regulations, not later than 18 months from date of enactment, pertaining to commercial motor vehicle safety. Such regulation shall establish minimum Federal safety standards for commercial motor vehicles and shall at a minimum, ensure that (1) commercial motor vehicles are safely maintained, equipped, loaded, and operated; (2) the responsibilities imposed upon operators of commercial motor vehicles do not impair their ability to operate such vehicles safely; (3) the physical condition of operators of commercial motor vehicles is such that they are able to operate such vehicles safely; and (4) the operation of commercial motor vehicles does not have deleterious effects on the physical condition of such operators.

The directive includes a prohibition against elimination or modification of any existing motor carrier safety rule pertaining exclusively to the maintenance, equipment, loading or operation (including routing regulations) of vehicles carrying materials found to be hazardous for the purposes of the Hazardous Materials Transportation Act (49 U.S.C. 1801 et seq.) unless and until an equivalent or more stringent regulation has been promulgated under the Hazardous Materials Transportation Act. We are seeking information, however, concerning the adoption of new or additional rules which may enhance the safety of hazardous materials transportation, as found in Part 397 of the FMCSR.

The Act also provides that after notice and opportunity for comment the Secretary may waive, in whole or in part, application of any regulation with respect to any person or class of persons, if it is determined that such waiver is not contrary to the public interest and is consistent with the safe operation of commercial motor vehicles. Any waiver granted shall be published in the **Federal Register** together with the reasons for such waiver.

This Advance notice of proposed rulemaking (ANPRM) is intended as the first step in implementing section 206 of the Motor Carrier Safety Act of 1984. It is the intention of the Bureau of Motor Carrier Safety to reissue the FMCSR (49 CFR Parts 390-399) under the Motor Carrier Safety Act of 1984 and under section 3102 of title 49, United States Code, as amended. This ANPRM outlines certain subjects or provisions of the FMCSR which will be considered for amendment prior to reissuance. Comment, however, is solicited on other areas which may require amendment in order to fulfill the Congressional purposes of the Motor Carrier Safety Act of 1984 outlined above.

The States are particularly requested to review this notice and the FMCSR in light of their own needs and experiences. Section 208 of the Motor Carrier safety Act of 1984 calls for the preemption of certain State rules on October 30, 1989 (1990 if extended by the Secretary). Section 207 of the Act provides for submission of all State commercial motor vehicle safety rules to the Secretary within 6 months for review and analysis with a view toward such preemption. While the purpose of the preemption provision is to achieve uniformity along the lines of the Federal rules, some States may have identified problems or solutions to problems which warrant consideration for nationwide application. Thus, States may wish to recommend specific changes which they believe will serve to also fulfill the purposes of the Motor Carrier Safety Act of 1984.

Excluded from this rulemaking is Part 393, Parts and Accessories Necessary for Safe Operation. Section 210 of the Act requires the Secretary to establish Federal standards for inspections of commercial motor vehicles and retention by employers of records of such inspections. It also directs the Secretary to initiate a rulemaking to afford interested parties an opportunity to comment on Part 393 and the inspection and retention procedures. A

separate rulemaking has been established relative to Part 393.

Also excluded from this rulemaking is Part 397, Transportation of Hazardous Materials; Driving and Parking Rules.

Comments are requested on the following areas that are being considered for revision:

Applicability

The applicability section being considered in Part 390 would include commercial motor vehicles operated in interstate or foreign commerce and: (1) Having a gross vehicle weight rating in excess of 10,000 pounds; (2) designed to transport more than 15 passengers including driver; or (3) transporting hazardous materials in a quantity requiring the vehicle to be placarded.

Consideration is also being given to include in the applicability section those employees and employers as defined in section 204 of the Act, as being subject to certain provisions of the FMCSR:

An "employee" means—

(1) An operator of a commercial motor vehicle (including an independent contractor while in the course of operating a commercial motor vehicle);

(2) A mechanic;

(3) A freight handler (helper); and

(4) Any individual other than an employer, who is employed by an employer and who in the course of his or her employment directly affects commercial motor vehicle safety, but such term does not include an employee of the United States, any State, or any political subdivision of a State who is acting within the course of such employment.

An "employer" means any person engaged in a business affecting interstate commerce who owns or leases a commercial motor vehicle in connection with that business, or assigns employees to operate it, but such term does not include the United States, any State, or political subdivision of a State.

There would be no need for an applicability chart as now appears in § 390.33, should the intracity operation exemption be eliminated, as being proposed herein.

Exemptions

Comments concerning the elimination of certain current regulatory exemptions are requested. Petitions for waiver of the application of the regulations, in whole or in part, would subsequently be considered. Waivers, authorized after notice and opportunity to comment, would be published in the **Federal Register** detailing the reasons for such waiver.

1. *School buses.* The Act directs the Secretary to waive application of the regulations to school buses unless the Secretary determines that making the regulations applicable to school buses is necessary for public safety. In making that determination, the Secretary must take into account all Federal and State laws applicable to such school buses. Comments concerning such a school bus waiver is specifically requested.

2. *Exempt intracity operation.* Consideration is being given to eliminate the exemption provided for vehicles and/or drivers used wholly within a municipality or the commercial zone thereof. Commercial zone operations today are considerably different from those operations conducted at the time the exemption was implemented. With the advent of high speed expressways and beltways through and around major cities, commercial zone operations are exposed to considerably heavier density traffic than that between distant cities. Comments are needed to support justification to warrant continuation of the exemption.

3. *Retail store deliveries—December 10 to December 25.* Section 395.3(c) of the FMCSR exempts from the hours of service regulations those drivers engaged solely in making deliveries for retail stores during the period from December 10 through December 25 each year. These types of operations are quite different today from those operations conducted years ago. Comments are requested concerning the refining of the definition of retail store deliveries with the possibility of eliminating the exemption.

4. *Lightweight vehicle exemption.* The Act defines a "commercial motor vehicle" as one having a gross vehicle weight rating of 10,001 pounds or more; one designed to transport more than 15 passengers, including the driver; or vehicles transporting hazardous materials in quantities requiring the vehicle to be placarded. Therefore, such an exemption would be irrelevant under the applicability provision.

5. *Contract mail carriers exemption.* Exemption provided for drivers of lightweight mail trucks, with a gross vehicle weight rating of 10,000 pounds or less, used exclusively to transport mail under contract with the U.S. Postal Service, would be irrelevant under the applicability provisions.

Other Areas Under Consideration

1. Section 206(a) of the Act requires regulations that will protect the safety and health of operators of commercial motor vehicles. Therefore, comments are requested concerning additional, more stringent employee safety and health standards with respect to work activities by employees of commercial motor carriers. Activities include those that are ordinarily and customarily performed in, on, or about motor vehicles, including but not limited to the operation, maintenance, loading and unloading of motor vehicles (See Docket MC–64 incorporated herein).

2. The National Transportation Safety Board has recommended a study of the feasibility of requiring drivers to have an additional national or State license or endorsement prior to driving vehicles containing bulk hazardous materials. It further recommended that the study should establish criteria for prior driving record and training in handling hazardous materials and in emergency procedures. Pending initiation of such a study, what additional, if any, requirements should be considered for drivers who operate commercial motor vehicles transporting hazardous materials in such quantities that requires the vehicle to be placarded.

3. Clarify the on-duty rule as it relates to the 60-hour or 70-hour weekly limitation. The current rule prohibits on-duty time following 60 hours on-duty in any 7 day period or 70 hours in any 8 day period. However, under a present interpretation, drivers may be on duty beyond the 60 or 70 hour limitation but may not drive. Safety of operation, to which the regulations are directed, is not compromised when a driver works in a non-driving capacity beyond the 60 or 70 hour limitation.

4. For the first time, the Act made private motor carriers of passengers subject to the provisions of the FMCSR. Since these carriers were never regulated there is no information or data readily available on which to make a determination as to the extent these carriers should be regulated. Comments are requested on whether a phase-in period of adjustment should be provided during which time the regulations would be made applicable on a limited basis. Should private motor carriers of passengers operating occasionally be made subject all of the FMCSR the same as the regulated carrier? Should the transportation of passengers by a commercial business enterprise, in furtherance of a primary business, be subject to all of the provisions of the FMCSR? Should the vehicle (bus) be maintained in accordance with all of the provisions of Part 393 parts and accessories and Part 396 inspection, repair and maintenance? Should the drivers be required to comply with the driver qualification requirements immediately or establish a step by step

approach over a period of several years? What paperwork requirements should the operators and drivers be required to comply with, or should they be exempt from the paperwork requirements except for accident reporting? To what extent should private carriage of passengers be regulated and what data is available to support that position?

Current Rulemaking Actions Incorporated Into This Docket

The following rulemaking actions are being closed and made a part of this docket. The comments submitted to those dockets listed below will be considered in conjunction with this rulemaking. Any person desiring to comment further to the following dockets may do so. Comments previously submitted need not be resubmitted.

• *MC–64—Employee Safety and Health Standards.*

The NPRM was published in the **Federal Register** March 2, 1978 (43 FR 8566), proposing safety and health standards to protect employees engaged in the operation, maintenance, loading and unloading of commercial motor vehicles and certain other employees. The standards were designed to eliminate uncertainty with regard to the jurisdictional authority of the Occupational Safety and Health Administration and the Federal Highway Administration.

• *MC–93—Migratory workers.*

An Advance Notice of Proposed Rulemaking (ANPRM) was published in the **Federal Register** August 4, 1980 (45 FR 51625). The notice solicited information concerning the transportaion of migrant workers as to what regulations, if any, should be added, modified or revoked.

• *MC–98—Exemptions—Operations Involving Retail Fertilizer Distribution to Farms.*

An ANPRM was published in the **Federal Register** February 4, 1982 (47 FR 5273). Comments were requested on a petition filed by The Fertilizer Institute to provide an exemption from the requirements of the FMCSR for operations involving direct retail sale and delivery of fertilizer to the farmer.

• *MC–99–1—Drivers Record of Duty Status.*

Comments submitted to the docket, due on or before January 31, 1985, will be considered along with any others submitted to this docket. Consideration will be given to the possible elimination of certain items required on the driver's record of duty status and extending the 12 hour limitation in the 100 mile radius exemption to 15 hours or permitting a 50 mile radius rule as an option with the 15 hour rule.

• *MC–100—Written Examination of Drivers.*

An ANPRM was published in the **Federal Register** Mrach 4, 1982 (47 FR 9256). Public comment was requested on the following options: (1) A pass/fail test requirement; (2) rescission of the requirement for the written examination; or (3) retention of the requirement as it is and update the questions.

• *MC–104—Qualifications of Drivers.*

An ANPRM was issued September 27, 1982 (47 FR 42383). Comments were requested on certain modifications recommended by the National Transportation Safety Board, including revison of the driver qualification provisions and development of specific information that a motor carrier must request from a driver applicant's former employer. A number of questions were presented with respect to modifications being considered.

• *MC–109—Reporting of Accidents.*

Comments submitted to this docket will be considered relative to the proposed accident form and the proposed increase from $2,000 to $4,000 as the minimum amount of property damage required for reporting of accidents.

Based upon the aforementioned discussion, the following rulemaking actions are hereby formally withdrawn: NPRM (3/2/78; 43 FR 8566; Docket MC–64), ANPRM (8/4/80; 45 FR 51625; Docket MC–93), ANPRM (2/4/82; 47 FR 5273), ANPRM (3/4/82; 47 FR 9256; Docket MC–100), ANPRM (9/27/82; 47 FR 42383; Docket MC–104), and NPRM (1/16/84; 49 FR 1912; Docket MC–109).

The FHWA has determined that this document contains neither a major rule under Executive Order 12291 nor a significant regulation under the regulatory policies and procedures of the Department of Transportation. This rulemaking action was initiated by a Congressional directive contained in section 206 of the Motor Carrier Safety Act of 1984. This ANPRM covers a broad regulatory spectrum and does not lend itself to a regulatory evaluation. Upon receipt and analysis of the comments to this ANPRM, separate dockets addressing specific Parts of the FMCSR are anticipated. We expect to prepare a full regulatory evaluation for each new docket established.

Based on the information available at this time, it is believed that any action taken in this rulemaking will not have a significant economic impact on a substantial number of small entities.

List of Subjects in 49 CFR Parts 390, 391, 392, 393, 394, 395, 396, 397, 398, 399

Motor carriers, Driver requirements, Driving motor vehicles, Parts and accessories, Accident reporting, Hours of service, Inspection, repair, and maintenance, Hazardous materials, Migrant workers, Employee safety and health.

(49 U.S.C. 3102; Pub. L. 98–554, 98 Stat. 2829, section 206; 49 CFR 1.48)

(Catalog of Federal Domestic Assistance Program Number 20.217, Motor Carrier Safety)

Issued on: January 16, 1985.

Kenneth L. Pierson,

Director, Bureau of Motor Carrier Safety.

[FR Doc. 85–1720 Filed 1–22–85; 8:45 am]

BILLING CODE 4910-22-M

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49 CFR Parts 392, 393, and 399

[BMCS Docket No. MC–80; and BMCS Docket No. MC–81; Notice No. 85–2]

Toxic Gases; Ambient Temperature in Truck Cabs

AGENCY: Federal Highway Administration. (FHWA), DOT.

ACTION: Withdrawal of notice of proposed rulemaking and withdrawal of advance notice of proposed rulemaking.

SUMMARY: The FHWA is withdrawing rulemaking actions on toxic gas concentrations found in truck cabs and alleged excessive in-cab heat, until such time research is undertaken to develop needed data to determine if further rulemaking is justified.

DATE: This withdrawal is effective January 23, 1985.

FOR FURTHER INFORMATION CONTACT: Mr. Neill L. Thomas, Bureau of Motor Carrier Safety, (202) 426–9767, or Mr. Thomas P. Holian, Office of the Chief Counsel, (202) 426–0346, Federal Highway Administration, 400 Seventh Street, SW., Washington, D.C. 20590. Office hours are from 7:45 a.m. to 4:15 p.m. ET, Monday through Friday.

SUPPLEMENTARY INFORMATION:

Toxic Gases in Commercial Motor Vehicles

On January 3, 1978 the FHWA published an Advance Notice of Proposed Rulemaking (ANPRM) in the **Federal Register** (43 FR 20) inviting comments and requesting information relative to toxic gases in truck cabs. The ANPRM was based on complaints and inquiries the FHWA had received alleging that toxic gas concentrations found in truck cabs existed at levels high

enough to be harmful to human health and well-being.

On June 18, 1979 the FHWA published a Notice of Proposed Rulemaking (NPRM) in the **Federal Register** (44 FR 34992) in response to the comments received. A revision to the Federal Motor Carrier Safety Regulations (FMCSR) was proposed setting definite exposure limits for three toxic gases within commercial motor vehicles. The intent, in establishing these limits, was to provide drivers with the same basic protection afforded industrial workers through current occupational safety and health standards as set by the Occupational Safety and Health Administration (OSHA).

Prior to publication of the ANPRM and NPRM, the FHWA sponsored a study measuring carbon monoxide (CO), nitric oxide (NO), and nitrogen dioxide (NO_2) in heavy duty truck cabs.[1] These gases were selected among the many components of exhaust, fuel, and crankcase sources because of their known presence and toxicity.

In the NPRM, it was proposed that the FHWA adopt requirements for these gases identical to those of the American Conference of Governmental Industrial Hygienists, a voluntary census organization. The proposed values for these gases were also essentially the same as those used by OSHA. The adoption of these standards by the FHWA was not considered to impose an undue burden on the motor carrier industry because the FHWA study indicated that well-maintained vehicles do not exceed these levels.

Docket Comments

Eleven commenters responded to the NPRM. Four commenters supported a regulation that specifies threshold values for toxic gas concentrations in cabs. These commenters included the International Brotherhood of Teamsters (IBT), General Drivers and Helpers Union Local 749, the University of Waterloo, and the Institute for Safety and Transportation.

The IBT commented that the values specified in the NPRM were not sufficient because they do not provide for the "additive effect" of two or more gases. The IBT indicated that the proposed values should reflect exposures in excess of 8 hours per day and 40 hours per week. The IBT recommended that the time weighted average (TWA) value for NO_2 be reduced. As a substitute, the IBT recommended the use of the exposure limits proposed by the National Institute of Occupational Safety and Health (NIOSH).

The General Drivers and Helpers Union commented that the problem they have encountered with truck fumes occurs when the exhaust exits underneath the tractor. They believe that the problem can be solved by providing an exhaust pipe that makes the exhaust fumes exit from above and behind the cab of the vehicle.

Six commenters were in opposition to the proposed regulation. These commenters included the American Truck Associations, Inc. (ATA), Private Truck Council of America, Inc. (PTCA), the Biscuit and Cracker Manufacturers' Association, General Motors Corporation, Reynolds Aluminum, and Kraft, Inc. The ATA commented that more research is needed to establish what a driver's long-term exposure actually is, taking into consideration that the concentration of gases in a cab will fluctuate.

Commenters in opposition stated that the proposed rule does not solve the problem of how the motor carrier is to measure these gases in the cab. The ATA commented that no procedure is provided for the motor carrier's measurement of NO and NO_2. Commenters wrote that compliance with this regulation would present a number of technical problems for the motor carrier. An example of this is the problem of controlling the ambient gas concentrations produced by outside sources, such as the exhaust of other vehicles or a driver's cigarette.

These commenters submitted that the rule would impose a significant burden on the motor carrier industry primarily because of the technical problems the motor carrier would encounter in complying with the rule as proposed. An example of this was provided by the ATA, in describing the equipment the motor carrier must have to measure gas concentrations:

> CO can be measured with a relatively simple Mines Safety Appliance carbon monoxide tester or similar device, however, the instrument error with such equipment is high, in the 20 percent range. NO_2 also can be checked with a "stained tube" type of device, but again incident of error is high. No similar, simple instrument is available to measure Nitric Oxide. A nondispersive infrared analyzer is needed. Such an analyzer, its calibration gases, and other related equipment are definitely not motor carrier shop appliances.[2]

The commenters believe that the problem of toxic gas concentrations can be addressed through stricter compliance with requirements already found in the FMCSR. Two examples are given: (1) Section 393.84, which provides that the floor of a cab must be free of unnecessary holes and be maintained to minimize the entrance of fumes and exhaust gases, and (2) § 393.94, which specifies maximum vehicle interior noise levels in truck cabs (49 CFR 393.84, 393.94).

Research

The study entitled "Toxic Gases in Heavy Duty Diesel Truck Cabs" recorded maximum gas concentrations from a worst-case selection of 88 vehicles. The concentrations recorded during idling and road testing were: Nitric oxide, 2 parts per million (ppm); nitrogen dioxide, 3 ppm; and carbon monoxide, 30 ppm. These measurements consisted of a combination of vehicle and outside air (ambient) concentrations. The proposed NIOSH nitrogen dioxide ceiling value of 1 ppm was exceeded by one-third of the vehicles when the levels in the surrounding air were added to those found in the cab. Worst-case nitrogen dioxide levels were found to be statistically correlated with exhaust leaks and closed cabs; testing showed that cab floor openings were the principal pathways for entrance of engine compartment gases.

Conclusion

Having analyzed the comments to the docket and reviewed the findings of the toxic gas study, it has been determined that there is insufficient data to support rulemaking at this time. Serious questions were raised as to the practicability of motor carriers being able to perform meaningful field measurements for CO, NO, and NO_2. The study found that the highest levels of toxic gas generated by the vehicles themselves did not reach the recommended ceiling values of NIOSH. For NO_2, the recommended NIOSH value of 1 ppm was exceeded by one-third of the vehicles when the ambient levels of the gas were included in the measurement. The highest value found for NO_2, was 3 ppm in the testing situation where the vehicle was idling with the windows and vents closed.

Because the study was conducted on worst-case vehicles, further research is needed to identify the concentration levels of the gases in a wider range of vehicles. In addition, information is needed to develop those testing procedures that can best be used to

[1] Toxic Gases in Heavy Duty Diesel Truck Cabs, available from the National Technical Information Service, Springfield, Virginia 22141, Accession No. PB-275957.

[2] Comments of American Trucking Associations, Inc. to BMCS Docket No. MC-80, August 17, 1979, p. 1-2. These comments are in the public docket and are available for review.

measure gas concentrations in the motor carrier environment.

The FHWA has determined that additional research is needed to justify further rulemaking in this area. Therefore, Docket No. MC–80 is hereby withdrawn.

Ambient Temperatures in Heavy Duty Truck Cabs

An ANPRM was published in the **Federal Register** on February 8, 1978 (43 FR 5397) inviting comments and requesting information relative to the ambient temperature and surface temperature in heavy duty truck cabs. The FHWA had received a number of complaints alleging excessive in-cab heat. The intent of the ANPRM was to obtain information that could answer the questions of whether the FHWA should regulate (1) maximum ambient temperature, (2) minimum ambient temperature, and (3) maximum temperature of exposed surfaces in truck cabs.

Docket Comments

Twenty-four commenters responded to the ANPRM. Five commenters supported a regulation that specified minimum and maximum ambient temperatures in truck cabs. These commenters included the IBT, Professional Drivers Council (PROD), and three drivers.

The IBT recommended a requirement prohibiting driver exposure to a time weighted average wet-bulb globe temperature (WBGT) of over 70° F. or below 64° F. The IBT recommended that the FHWA discover simpler measurement techniques that could be substituted for the WBGT. The PROD recommended a standard prohibiting driver exposure to temperatures exceeding 76° F. (WGBT) for one hour. They, too, recommended that measurement procedures be developed that could replace the WGBT measurement in the truck cab.

Eighteen commenters opposed any minimum or maximum ambient temperature regulation for truck cabs. These commenters included the ATA, Motor Vehicle Manufacturers Association (WVMA) PTCA, the International Mobil Air Conditioning Association, Inc., and the American Petroleum Institute. Seven vehicle manufacturers, three air-conditioning companies, two motor carriers, and Sea-Land Service, Inc. submitted comments to the docket.

These commenters believe that the need for a requirement in this area has not been demonstrated. The manufacturers maintain that the market for truck-tractors continues to place emphasis on comfort in the driver's environment. The example given was the National Master Freight Agreement which specifies that newly-manufactured vehicles added to the road fleet after April 1, 1977 must be air-conditioned. The ATA indicated that the Agreement also specifies that cabs must have heaters, and § 393.79 of the FMCSR specifies that cabs must have a defrosting device (49 CFR 393.79). The commenters indicated that complaints about hot surfaces in cabs are not widespread and can be easily handled through working with the vehicle manufacturers.

The commenters indicated that specifying ambient temperature levels in the truck cab would impose a significant burden on the motor carrier industry. They believe that such a regulation, in the effect, would require motor carriers to install air conditioners on all vehicles. The ATA commented that along with the costs in obtaining air conditioners, the maintenance costs could be significant, particularly for companies whose operations do not justify air conditioner use.

Commenters agreed that extreme heat stress can significantly affect driver performance. The ATA maintained, however, that because of the nature of truck operation and vehicle design, the driver has the opportunity to control air flow into the cab. Therefore, truck environment cannot be strictly compared to factory environment. Commenters contended that, depending on the motor carrier operation, the driver will be exposed to varying ambient temperatures in different parts of the United States. Because no two truck operations will encounter identical temperature conditions, commenters believe that one regulatory standard in this area is not feasible and the problem of extreme heat in the cab can best be solved through labor-management cooperation.

Conclusion

The FHWA has determined that the need for ambient temperature regulations has not been demonstrated at this time. Serious questions were raised as to the practicability of mandating allowable temperature levels in the cab when the commerical motor vehicle may be operated over a wide geographical location, and under many variations in ambient temperature.

Mandating a maximum ambient temperature could impose significant operating costs on large portions of the motor carrier industry. The FHWA agrees that until further research identifies a widespread problem with in-cab heat, the issue of maintaining a comfortable cab temperature should remain with the motor carrier, driver, and vehicle manufacturer. Therefore, Docket No. MC–81 is hereby withdrawn.

The FHWA has determined that this document contains neither a major rule under Executive Order 12291 nor a significant regulation under the regulatory policies and procedures of the Department of Transportation.

Under the criteria of the Regulatory Flexibility Act, it is certified that this action will not have a significant economic impact on a substantial number of small entities.

(49 U.S.C. 3102; 49 CFR 1.48)

(Catalog of Federal Domestic Assistance Program Number 20.217, Motor Carrier Safety)

Issued on: January 16, 1985.

Kenneth L. Pierson,

Director, Bureau of Motor Carrier Safety.

[FR Doc. 85–1721 Filed 1–22–85; 8:45 am]

BILLING CODE 4910-22-M

INTERSTATE COMMERCE COMMISSION

49 CFR Part 1152

[Ex Parte No. 274 (Sub-11)]

Abandonment Regulations Costing

AGENCY: Interstate Commerce Commission.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Commission's regulations at 49 CFR Part 1152 govern applications to abandon or discontinue service over rail lines and offers of financial assistance. The general purpose of the proposed changes is to permit a more accurate determination of the costs of rail operation in connection with rail abandonment and subsidy proceedings. We propose to modify the standards for determining costs, revenues, and return on value contained in Subpart D of the regulations. Specifically, (1) we propose to distinguish the economic costs of operation from actual avoidable costs of operation; (2) we intend to modify computation of the rate of return used to determine economic costs, and we seek comments on a number of issues concerning implementation of the revised methodology; and (3) we propose to incorporate some of the Regional Subsidy Standards (49 CFR Part 1155). We invite comments on the merits of the specific proposals, and on whether the more detailed costs calculations necessitated by these changes impose an unreasonable

accounting burden on parties to rail abandonment and subsidy proceedings.

DATES: Comments must be filed by March 25, 1985.

ADDRESSES: Send comments (original and 5 copies) referring to Ex Parte No. 274 (Sub-11) to:

Office of the Secretary, Case Control Branch, Interstate Commerce Commission, Washington, DC 20423.

FOR FURTHER INFORMATION CONTACT:

Louis E. Gitomer, (202) 275–7245;
Wayne A. Michel, (202) 275–7657;
or
Thomas B. Shick, (202) 275–7972.

SUPPLEMENTARY INFORMATION: The Commission's regulations at 49 CFR Part 1152 govern applications to abandon or discontinue service over rail lines and offers of financial assistance. The general purpose of the proposed changes is to permit a more accurate determination of the costs of rail operation in connection with rail abandonment and subsidy proceedings. We propose to modify portions of Subpart D of the regulations that set forth standards for determining costs, revenues, and return on value. Specifically, we propose to combine in a single section and provide a uniform method for computing all "economic costs" associated with abandonment and subsidy proceedings, i.e., return on investment in rail cars and locomotives, and opportunity costs. Also, in Ex Parte No. 274 (Sub-No. 3C), *Abandonment of R. Lines—Use of Opportunity Costs*, 1 I.C.C. 2d ———, served December 28, 1984, we adopted a revised procedure for more accurately computing the "real" (inflation adjusted) rate of return for opportunity costs determinations. we intend to adopt that methodology for use in all "economic cost" determinations, and invite comment on a number of issues concerning its implementation. Further, we propose to expand the asset base for computing economic costs to include current income tax benefits and working capital. We also propose to adopt for use in abandonment and subsidy proceedings certain changes recently made in the Regional Subsidy Standards, 49 CFR Part 1155. Specifically, we propose to (a) allocate train supply and expense accounts on a combined car-mile/carload basis; (b) apportion locomotive fuel costs on the basis of fuel cost per locomotive unit hours data published by the General Managers Association (GMA), (c) adopt an improved method of adjusting off-branch and certain on-branch cost accounts for inflation, (d) adopt an improved method of developing off-branch costs for classes II and III railroads, (e) clarify the regulations to assure that carriers do not include both an administrative fee and administrative expenses in subsidy calculations, and (f) provide that avoidable costs of providing service on a branch will not exceed those necessary for an honest and efficient operation.

Additional information is contained in the Commission's full decision. To purchase a copy of the full decision, contact T.S. InfoSystems, Inc., Room 2227, Interstate Commerce Commission, Washington, DC 20423, or Call 289–4357 (DC Metropolitan area) or toll free (800) 424–5403.

This action will not significantly affect either the quality of the human environment or energy conservation. This rule will not have a significant economic impact on a substantial number of small entities because the general purpose of the proposed changes is to permit a more accurate determination of the economic costs of rail operations in connection with rail abandonment and subsidy proceedings.

List of Subjects in 49 CFR Part 1152

Administrative practice and procedures, Railroads.

This rulemaking is issued under the authority of 49 U.S.C. 10321, 10362, 10903, 10904, and 10905, and 5 U.S.C. 553.

Dated: January 11, 1985.

By the Commission, Chairman Taylor, Vice Chairman Andre, Commissioners Sterrett, Gradison, Simmons, Lamboley, and Strenio. Vice Chairman Andre dissented with a separate expression.

James H. Bayne,

Secretary.

[FR Doc. 85–1691 Filed 1–22–85; 8:45 am]

BILLING CODE 7035-01-M

Notices

Federal Register
Vol. 50, No. 15
Wednesday, January 23, 1985

This section of the FEDERAL REGISTER contains documents other than rules or proposed rules that are applicable to the public. Notices of hearings and investigations, committee meetings, agency decisions and rulings, delegations of authority, filing of petitions and applications and agency statements of organization and functions are examples of documents appearing in this section.

DEPARTMENT OF AGRICULTURE

Forest Service

Humboldt National Forest, Grazing Advisory Board; Meeting

The Humboldt National Forest Grazing Advisory Board will meet on February 28, 1985 at 10:00 a.m. p.s.t., at the Supervisor's Office, 976 Mountain City Highway, Elko, Nevada.

The meeting is open to the public.

The purpose of the meeting is to discuss:

1. Allotment management planning.
2. Utilization of Range Betterment Fund.

Dated: January 3, 1985.

B.J. Graves,

Forest Supervisor.

[FR Doc. 85–1667 Filed 1–22–85; 8:45 am]

BILLING CODE 3410-11-M

Ochoco National Forest Grazing Advisory Board; Meeting

The Ochoco National Forest Grazing Advisory Board will meet at 10:00 a.m., April 19, 1985, in the Forest Supervisor's Office, Federal Building, Prineville, Oregon.

The purpose of this meeting is to discuss subjects concerning the development of allotment management plans and utilization of range betterment funds as presented by board members, permittees, and the general public.

The meeting will be open to the public. Persons who wish to attend should notify Jack Royle, P.O. Box 490, Prineville, Oregon 97754; phone (503) 447–6247. Written statements may be filed with the committee before or after the meeting.

Dated: January 14, 1985.

Dave Rittersbacher,

Forest Supervisor.

[FR Doc. 85–1675 Filed 1–22–85; 8:45 am]

BILLING CODE 3410-11-M

Establishment of Purchase Units and Change in Boundary of Ouachita National Forest

Pursuant to authority invested in me by section 11 of the Act of March 1, 1911 (36 Stat. 961) as amended, and the delegation of authority and assignment of functions by the Secretary of Agriculture to the Asssistant Secretary of Agriculture for Natural Resources and Environment, purchase units are established and the boundary of the Ouachita National Forest is extended as described below and all lands within the Ouachita National Forest as adjusted, that have been acquired by the United States and which by statute attain status as National Forest land subject to the Act of March 1, 1911, are hereby designated for administration as part of the Ouachita National Forest.

Ouachita National Forest, Arkansas, Fifth Principal Meridian

Ashley County

T. 19 S., R. 8 W.,
Sec. 21, less the following described tract in the SW¼SW¼: Beginning at the NW corner of the SW¼SW¼ of Section 21, T. 19 S., R. 8 W., running thence due North 1 chain 15 links to the NW corner of the church property, thence East 6 chains 29 links, South 8 chains 42 links, West 6 chains 28 links, and thence North 7 chains 27 links to the point of beginning and containing 5.29 acres, more or less;
Sec. 22, W½;
Sec. 27, NW¼, N½SW¼;
Sec. 28, N½, N½S½;

Containing in the aggregate 1,674.71 acres more or less, and known as the Crossett Experimental Forest:

Saline County

T. 1 N., R. 17 W.,
Sec. 3, NW¼SW¼,

Containing 40.00 acres more or less;

Yell County

T. 3 N., R. 23 W.,
Sec. 20, SW¼NW¼ lying North of the Fourche LaFave River.

Containing 4.00 acres more or less.

Ouachita National Forest, Oklahoma, Indian Meridian

LeFlore County

T. 3 N., R. 26 E.,
Sec. 12, NW¼NE¼,

Containing 40.00 acres or less;

McCurtain County

T. 7 S., R. 25 E.,
Sec. 20, NW¼NW¼ lying North of Little River,
T. 9 S., R. 25 E.,
Sec. 25, N½NE¼NE¼.

Effective date: This order shall become effective January 23, 1985.

Dated: January 15, 1985.

John B. Crowell, Jr.,

Assistant Secretary for Natural Resources and Environment.

[FR Doc. 85–1722 Filed 1–22–85; 8:45 am]

BILLING CODE 3410-11-M

Soil Conservation Service

Copper Creek Watershed, Virginia; Finding of No Significant Impact

AGENCY: Soil Conservation Service, USDA.

ACTION: Notice of Finding of No Significant Impact.

SUMMARY: Pursuant to section 102(2)(C) of the National Environmental Policy Act of 1969; the Council on Environmental Quality Guidelines (40 CFR Part 1500); and the Soil Conservation Service Guidelines (7 CFR Part 650); the Soil Conservation Service, U.S. Department of Agriculture, gives notice that an environmental impact statement is not being prepared for the Copper Creek Wateshed, Scott and Russell Counties, Virginia.

FOR FURTHER INFORMATION CONTACT: Manly S. Wilder, State Conservationist, Soil Conservation Service, 400 North Eighth Street, Federal Building, Richmond, Virginia 23240, telephone 804–771–2455.

SUPPLEMENTARY INFORMATION: The environmental assessment of this federally assisted action indicates that the project will not cause significant local, regional, or national impacts on the environment. As a result of these findings, Manly S. Wilder, State Conservationist, has determinated that the preparation and review of an

environmental impact statement are not needed for this project.

The project concerns a plan for watershed protection. The recommended plan includes soil conservation practices and critical area treatment on 19,637 acres of cropland, pastureland, and woodland. Primary effects of the plan include decreased erosion and sedimentation on agricultural lands, improved economic and social aspects, and improved water quality.

A public meeting will be held at the Nickelsville Elementary School, Nickelsville, Virginia, on February 28 at 7 p.m.

The Notice of a Finding of No Significant Impact (FONSI) has been forwarded to the Environmental Protection Agency and to various Federal, State and Local agencies and interested parties. A limited number of copies of the FONSI are available to fill single copy requests at the above address. Basic data developed during the environmental assessment are on file and may be reviewed by contacting Gerald P. Bowie.

No administrative action on implementation of the proposal will be taken until 30 days after the date of this publication in the **Federal Register**.

(Catalog of Federal Domestic Assistance Program No. 10.904, Watershed Protection and Flood Prevention Program. Office of Management and Budget Circular A-95 regarding State and local clearinghouse review of Federal and federally assisted programs and projects is applicable)

Manly S. Wilder,

State Conservationist.

January 14, 1985.

[FR Doc. 85-1674 Filed 1-22-85; 8:45 am]

BILLING CODE 3410-16-M

Fishing Creek Watershed; Granville County, NC

AGENCIES: North Carolina Department of Natural Resources and Community Development and the U.S. Department of Agriculture, Soil Conservation Service.

ACTION: Notice of finding of no significant impact.

SUMMARY: Pursuant to section 102(2)(C) of the National Environmental Policy Act of 1969; the Council on Environmental Quality Guidelines (40 CFR Part 1500); and the Soil Conservation Service Guidelines (7 CFR Part 650); the Division of Soil and Water Conservation, North Carolina Department of Natural Resources and Community Development and the Soil Conservation Service, U.S. Department of Agriculture, give notice that an environmental impact statement is not being prepared for the Fishing Creek Watershed, Granville County, North Carolina.

FOR FURTHER INFORMATION CONTACT: Billy Ray Hall, Acting Division Director, North Carolina Department of Natural Resources and Community Development, Post Office Box 27687, Raleigh, North Carolina 27611, telephone 919 733-4984 or Coy A Garrett, State Conservationist, Soil Conservation Service, 310 New Bern Avenue, Room 535, 5th Floor Federal Building, Raleigh, North Carolina 27601, telephone 919 755-4210.

SUPPLEMENTARY INFORMATION: The environmental assessment of this federally assisted action indicates that the project will not cause significant local, regional, or national impacts on the environment. As a result of these findings, Coy A. Garrett, State Conservationist, has determined that the preparation and review of an environmental impact statement are not needed for this project.

The project concerns a plan for flood control and watershed protection. The planned works of improvement include accelerated technical and financial assistance to apply land treatment measures on 3,725 acres of cropland.

The Notice of A Finding of No Significant Impact (FONSI) has been forwarded to the Environmental Protection Agency and to various federal, state, and local agencies and interested parties. A limited number of copies of the FONSI are available to fill single copy requests at the above address. Basic data developed during the environmental assessment are on file and may be reviewed by contacting Billy Ray Hall.

No administrative action on implementation of the proposal will be taken until 30 days after the date of this publication in the **Federal Register**.

(Catalog of Federal Domestic Assistance Program No. 10.904, Watershed Protection and Flood Prevention Program. Office of Management and Budget Circular A-95 regarding state and local clearinghouse review of federal and federally assisted programs and projects is applicable)

Dated: January 10, 1985.

George C. Norris,

Deputy State Conservationist.

[FR Doc. 85-1670 Filed 1-22-85; 8:45 am]

BILLING CODE 3410-16-M

DEPARTMENT OF COMMERCE

National Bureau of Standards

National Bureau of Standards Visiting Committee; Meeting

Pursuant to the Federal Advisory Committee Act, 5 U.S.C. App., notice is hereby given that the National Bureau of Standards Visiting Committee will meet on Wednesday, February 6, 1985, from 9:00 a.m. to 5:15 p.m. in Lecture Room B, Administration Building, National Bureau of Standards, Gaithersburg, Maryland.

The NBS Visiting Committee is composed of five members prominent in the fields of science and technology and appointed by the Secretary of Commerce.

The purpose of the meeting is to review the efficiency of the Bureau's scientific work and the condition of its equipment in order to assist the Committee in reporting to the Secretary of Commerce as required by law.

The public is invited to attend, and the Chairman will entertain comments or questions at an appropriate time during the meeting. Any person wishing to attend the meeting should inform Mrs. Carolyn Goodfellow, Office of Research and Technology Applications, National Bureau of Standards, Gaithersburg, Maryland 20899, telephone (301) 921-2226.

Dated: January 15, 1985.

Ernest Ambler,

Director.

[FR Doc. 85-1657 Filed 1-22-85; 8:45 am]

BILLING CODE 3510-13-M

[Docket No. 30812-161]

Approval of Federal Information Processing Standard 1-2, Code for Information Interchange, Its Representations, Subsets, and Extensions

AGENCY: National Bureau of Standards, Commerce.

ACTION: Correction of Federal Information Processing Standard 1-2, Code for Information Interchange, Its Representations, Subsets, and Extensions.

SUMMARY: The purpose of this notice is to provide the correct text for Federal Information Processing Standard 1-2. Notice of the approval of this standard by the Secretary of Commerce was announced in the **Federal Register** of November 14, 1984 (49 FR 45041-45044). Paragraph 2 of the Explanation Section of FIPS 1-2 was omitted from the

version printed in the November 14, 1984 notice. Minor editorial modifications to accommodate the insertion of that paragraph have been made.

FIPS PUB 1–2 consolidates and supersedes five existing FIPS standards. The superseded standards are FIPS PUBS 1–1, 7, 15, 35, and 36. This consolidation reduces the number of closely related FIPS PUBS in the family of standards based upon the voluntary American National Standard Code for Information Interchange (ASCII). A revision to FIPS PUB 2, Perforated Tape Code for Information Interchange, was also announced in the **Federal Register** of November 14, 1984 (49 FR 45044–45045).

In consolidating the provisions of FIPS 1–1, 35, 36, this revised standard adopts in whole three American National Standards: X3.4–1977, Code for Information Interchange (ASCII); X3.32–1973, Graphic Representation of the Control Characters of American National Standard Code for Information Interchange; and X3.41–1974, Code Extension Techniques for Use with the 7-Bit Coded Character Set of American National Standard Code for Information Interchange.

The document which was presented to the Secretary, is part of the public record and is available for inspection and copying in the Department's Central Reference and Records Inspection Facility, Room 6628, Herbert C. Hoover Building, 14th Street between Pennsylvania and Constitution Avenues NW., Washington, DC 20230.

The approved standard contains two portions: (1) An announcement portion which provides information concerning the applicability, implementation, and maintenance of the standard and (2) a specifications portion which deals with the technical requirements of the standard. Only the announcement portion of the revised standard is provided in this notice.

FIPS PUB 1–2 continues to specify the same three subsets of ASCII graphic characters that are detailed in FIPS PUB 15, and it also encompasses, simplifies, and replaces the implementation instructions currently prescribed in FIPS PUB 7.

FIPS PUB 1–2 became effective on November 14, 1984.

ADDRESS: Interested parties may purchase copies of this revised standard, including the technical specifications portions, from the National Technical Information Service (NTIS). Specific ordering information from NTIS for this revised standard is set out in the Where to Obtain Copies Section of the announcement portion of the standard.

FOR FURTHER INFORMATION CONTACT: Mr. John L. Little, Center for Computer Systems Engineering, Institute for Computer Sciences and Technology, National Bureau of Standards, Gaithersburg, MD 20899, (301) 921–3723.

Dated: January 15, 1985.

Ernest Ambler,

Director.

Federal Information Processing Standards Publication 1–2

[FIPS PUB 1–2 Supersedes FIPS PUBS 1–1, 7, 15, 35, and 36]

Announcing the Standard for Code for Information Interchange, Its Representations, Subsets, and Extensions

Federal Information Processing Standards Publications are issued by the National Bureau of Standards pursuant to section 111(f)(2) of the Federal Property and Administrative Services Act of 1949, as amended, Pub. L. 89–306 (79 Stat. 1127; 40 U.S.C. 759(f)), Executive Order 11717 (38 FR 12315, dated May 11, 1973), and Part 6 of Title 15, Code of Federal Regulations (CFR).

Name of Standard

Code for Information Interchange, Its Representations, Subsets, and Extensions. (The Code for Information Interchange is commonly known as ASCII (pronounced "as'key"), an acronym for American Standard Code for Information Interchange.)

Category of Standard

Hardware and Software Standard.

Subcategory

Interchanges Codes, Media, and Data Files.

Explanation

This standard specifies a coded character set and a recommended collating sequence, subsets, extensions, and certain graphic representations for the set, all for use in Federal information processing systems, communications systems, and related equipment, that are procured by the Federal Government. Related equipment includes all character-oriented devices and media, such as printers, teleprinters, display devices, keyboards, magnetic tape in the form of reels, cassettes or cartridges, flexible disks, optical or magnetic character readers and printers or embossers, punched cards, perforated tape, or other interchangeable media that are produced for input to a computer based system or received as output from a computer based system. The standard also applies to the data interchanged in or through such systems and equipment. Data systems to which this standard is applicable include any structured arrangement of character-oriented records, files, or indices.

This Federal ADP standard does not extend to the internal structure of the central processing unit or peripheral devices. In general, therefore, computers may operate in any mode and use any internal code which the equipment manufacturer deems most efficient.

Additional control functions for many types of equipment such as character imaging devices are given in FIPS PUB 86, Additional Controls for Use with ASCII. Instructions for implementing the standard code and its extensions, in various media, are given in other FIPS PUBS cited below in the section on "Related Documents." Information concerning the use of this standard in communications system that are a part of the National Communications Systems may be obtained from the Manager, National Communications System, Attention: NCS–O, Washington, D.C. 20305.

Approving Authority

Secretary of Commerce.

Maintenance Authority

Department of Commerce, National Bureau of Standards (Institute for Computer Sciences and Technology).

Cross Index

a. American National Standard X3.4–1977, Code for Information Interchange (ASCII).

b. American National Standard X3.32–1973, Graphic Representation of the Control Characters of American National Standard Code for Information Interchange.

c. American National Standard X3.41–1974, Code Extension Techniques for Use with the 7-Bit Coded Character Set of American National Standard Code for Information Interchange.

Related Documents

a. International Standard ISO 646–1983, 7-Bit Coded Character Set for Information Interchange.

b. CCITT Recommendation V.3, 1972, International Alphabet No. 5.

c. International Standard ISO 4873–1979, 8-Bit Coded Character Set for Information Interchange.

d. International Standard ISO 2022–1982, Code Extension Techniques for Use with the ISO 7-Bit Coded Character Set.

e. International Standard ISO 2375–1974, Procedure for Registration of Escape Sequences.

f. American National Standard X3.64–1979, Additional Controls for Use with American National Standard Code for Information Interchange.

g. International Standard ISO 6429–1983, Additional Control Functions for Character Imaging Devices.

h. American National Standard X3.28–1976, Procedures for the Use of the Communication Control Characters of American National Standard Code for Information Interchange in Specified Data Communication Links.

i. American National Standard X3.57–1977, Structure for Formatting Message Headings for Information Interchange using the American National Standard Code for Information Interchange for Data Communication System Control.

j. American National Standard X4.23–1982, Keyboard Arrangements for Alphanumeric Machines.

k. FIPS PUB 2–1, Perforated Tape Code for Information Interchange (adopts ANSI X3.6–1965, reaffirmed in 1983).

l. FIPS PUB 3–1, Recorded Magnetic Tape for Information Interchange (800 CPI, NRZI) (adopts ANSI X3.22–1973).

m. FIPS PUB 14–1, Hollerith Punched Card Code (adopts ANSI X3.26–1980).

n. FIPS PUB 16–1, Bit Sequencing of the Code for Information Interchange in Serial-by-Bit Data Transmission (adopts ANSI X3.15–1976).

o. FIPS PUB 17–1, Character Structure and Character Parity Sense for Serial-by-Bit Data Communication in the Code for Information Interchange (adopts ANSI X3.16–1976).

p. FIPS PUB 18–1, Character Structure and Character Parity Sense for Parallel-by-Bit Data Communication in the Code for Information Interchange (adopts ANSI X3.25–1976).

q. FIPS PUB 25, Recorded Magnetic Tape for Information Interchange (1600 CPI, Phase Encoded) (adopts ANSI X3.39–1973).

r. FIPS PUB 32–1, Optical Character Recognition Character Sets (adopts ANSI X3.17–1977 for OCR–A and ANSI X3.49–1975 for OCR–B).

s. FIPS PUB 33–1, Character Set for Handprinting (adopts ANSI X3.45–1982).

t. FIPS PUB 50, Recorded Magnetic Tape for Information Interchange, 6250 cpi (246 cpmm), Group Coded Recording (adopts ANSI X3.54–1976).

u. FIPS PUB 51, Magnetic Tape Cassettes for Information Interchange (3.810 mm [0.150 inch] Tape at 32 bpmm [800 bpi], Phase Encoded) (adopts ANSI X3.48–1977).

v. FIPS PUB 52, Recorded Magnetic Tape Cartridge for Information Interchange, 4-Track, 6.30 mm (¼ inch), 63 bpmm (1600 bpi), Phase Encoded (adopts ANSI X3.56–1977).

w. FIPS PUB 79, Magnetic Tape Labels and File Structure for Information Interchange (adopts ANSI X3.27–1978 with qualifications).

x. FIPS PUB 86, Additional Controls for Use with American National Standard Code for Information Interchange (adopts ANSI X3.64–1979).

y. FIPS PUB 91, Magnetic Tape Cassettes for Information Interchange, Dual Track Complementary Return-to-Bias (CRB) Four-States Recording on 3.81-mm (0.150-in) Tape (adopts ANSI X3.59–1981).

z. FIPS PUB 93, Parallel Recorded Magnetic Tape Cartridge for Information Interchange, 4-Track, 6.30 mm (¼ inch), 63 bpmm (1600 bpi), Phase Encoded (adopts ANSI X3.72–1981).

aa. ISO International Register of Character Sets to be Used with Escape Sequences, maintained and available without charge from the Registration Authority for ISO 2375 (Related Document e. above): European Computer Manaufacturers Association (ECMA), Rue du Rhone 114, CH–1204 Geneva, Switzerland (the mailing address must include a specific name of a person in each agency requesting a copy of the register and its updates which are issued by ECMA as new sets become registered).

Applicability

This standard is applicable to Federal acquisition and use of data processing or communication systems, data systems, system components, and related equipment that may be required to interchange character coded information, or represent control characters.

Implementation

All equipment and coded character information to which this standard is applicable that is brought into the Federal Government inventory on or after the November 14, 1984 effective date of this FIPS PUB must be in conformance with this standard unless a waiver has been obtained in accordance with the waiver provisions given below. The superseded FIPS PUBS still apply according to their terms to systems, equipment and information obtained before the effective date of this FIPS PUB.

More efficient use of magnetic tape and other media for locally maintained installation files is sometimes realized by the use of non-standard techniques (e.g., packed numerics, floating point, pure binary). Where interchange of information external to the immediately local environment is not a consideration, local use of such techniques may be employed without a waiver.

The use of subsets of fewer than the 128 characters of ASCII must be in accordance with the section on the specification of subsets included in this FIPS PUB. The use of extended sets in 7-bit form employing alternate assignments of the 128 binary patterns of ASCII must be accomplished in accordance with ANSI X3.41 which also is adopted by this FIPS PUB. The use of expanded sets in 8-bit form, having 256 binary patterns available, must also be accomplished in accordance with ANSI X3.41. Extended and expanded sets, wherever possible, must be in conformance with a set registered in the ISO international Register of Character Sets to be Used with Escape Sequences as noted in Related Document aa.

Additional control functions for character-oriented equipment and data systems are now governed by FIPS PUB 86.

Specifications

This standard adopts in whole three American National Standards:

a. American National Standard X3.4–1977, Code for Information Interchange (ASCII).

b. American National Standard X3.32–1973, Graphic Representation of the Control Characters of American National Standard Code for Information Interchange.

c. Amercian National Standard X3.41–1974, Code Extension Techniques for Use with the 7-Bit Coded Character Set of American National Standard Code for Information Interchange.

This standard also specifies three graphic character subsets of ASCII, in "Specifications for Subsets of the Standard Code for Information Interchange," included in this FIPS PUB. The three subsets are:

Figure 1—95-Character Graphic Subset
Figure 2—64-Character Graphic Subset
Figure 3—16-Character Graphic Numeric Subset.

These three subsets are derived from the 128-character set of the American National Standard Code for Information Interchange (ASCII, ANSI X3.4–1977).

In order to facilitate the interchange of data and equipment at the subset level within the Federal government, it is essential to limit the use of subsets to the three described in this FIPS PUB. Each subset is intended to be used in those applications whose needs are adequately served by that subset.

Waivers

If instances arise in which an agency cannot comply with the provisions of this FIPS PUB, the head of the agency is authorized to waive its application.

Generally, two conditions apply in those exceptional cases which would warrant a waiver:

a. Significant, continuing cost or efficiency disadvantages will be encountered by the use of this standard and,

b. The interchange of information with other systems is not anticipated.

Notification of approved waivers shall be sent to the Director, Institute for Computer Sciences and Technology, National Bureau of Standards, Gaithersburg, MD 20899.

Special Information

FIPS PUB 1, Code for Information Interchange, was first issued in 1968, adopting the then current ASCII standard, X3.4–1968, except for the so-called "New Line option." The first revision, FIPS PUB 1–1, was issued in 1980, adopting in whole the current version of ASCII, ANSI X3.4–1977, including the New Line option. FIPS PUB 7, Implementation of the Code for Information Interchange and Related Media Standards, was published in 1969 and was in effect until it was superseded by the issuance of this FIPS PUB 1–2. FIPS PUB 7 did not adopt a standard, but was developed to provide implementation guidance for Federal agencies. FIPS PUB 15, Subsets of the Standard Code for Information Interchange, was issued in 1971 and was based in part upon a draft voluntary standard for graphic subsets of ASCII which has not since been approved as an American National Standard; as a consequence, the specifications for subsets of ASCII are not available as an ANSI publication but are included as a section of this document. FIPS PUB 35, Code Extension Techniques in 7 or 8 Bits, was issued in 1975, adopting in whole ANSI X3.41–1974. FIPS PUB 36, Graphic Representation of the Control Characters of ASCII, was also issued in 1975, adopting in whole ANSI X3.32–1973. Section 8 of FIPS PUB 7 discusses the use of subsets, extended sets (in 7 bits), expanded sets (in 8 bits) and registration of extended and expanded sets by NBS. Since adoption of FIPS PUB 7, NBS has not registered any such sets. Subsequently, an international registry of character sets to be used with ISO 646 (similar to ASCII) Escape sequences has been established. The international Registration Authority is currently the European Computer Manufacturers Association (ECMA). See Related Document aa. above.

Where to Obtain Copies

Copies of this publication are available for sale from the National Technical Information Service, U.S. Department of Commerce, Springfield, Virginia 22161. (Sale of the American National Standards adopted by the specifications provision of this standard is by arrangement with the American National Standards Institute.) When ordering, refer to Federal Information Processing Standards Publication 1–2 (FIPSPUB1–2), and title. Payment may be made by check, money order, or deposit account.

Ordering information for the ISO International Register of Character Sets to be Used with Escape Sequences, is provided in paragraph aa of the Related Documents provision.

Additional Provision Specifyng Subsets

The final printed version of FIPS 1–2 will include a section entitled: "Specifications for Subsets of the Standard Code for Information Interchange." This provision will contain all of the technical information from the specifications portion of FIPS PUB 15, which is being superseded by FIPS PUB 1–2. Minor editorial changes will be made to update the specifications portion of FIPS PUB 15.

[FR Doc. 85–1658 Filed 1–22–85; 8:45 am]

BILLING CODE 3510–13–M

National Oceanic and Atmospheric Administration

National Marine Fisheries Service; Issuance of General Permits; Japan Deep Sea Trawlers Assn., et al.

On January 2, 1985, general permits to incidentally take marine mammals during commercial fishing operations in 1985 were issued to:

1. The Japan Deep Sea Trawlers Association, No. 601 Daito Buiding, 3–6, Kandaogawacho, Chiyodaku, Tokyo, Japan, in Category 1: Towed and Dragged Gear to take 90 northern sea lions, 5 northern fur seals, 25 harbor seals, and a total of 15 cetaceans of the following species: pilot whale, Atlantic harbor porpoise, and Atlantic white-sided dolphin.

2. The Hokuten Trawlers Association, Toranomon Chuo Building, 1–16, Toranomon, 1, Minatoku, Tokyo, Japan, in Category 1: Towed and Dragged Gear, to take 45 northern sea lions, 5 northern fur seals, and 5 harbor seals.

3. The North Pacific Longline-Gillnet Association, Zenkeiren Building, 2–7–2, Hirakawa-cho, Chiyodaku, Tokyo, Japan, in Category 5: Other Gear to take by harassment only.

All takings are incidental to commercial fishing operations within the United States Fishery Conservation Zone, pursuant to 50 CFR 214.24 (45 FR 72187–72196).

These general permits are available for public review in the Office of the Assistant Administrator for Fisheries, 3300 Whitehaven Street, NW., Washington, D.C.

Dated: January 15, 1985.

Richard B. Roe,

Director, Office of Protected Species and Habitat Conservation, National Marine Fisheries Service.

[FR Doc. 85–1671 Filed 1–22–85; 8:45 am]

BILLING CODE 3510–22–M

COMMITTEE FOR THE IMPLEMENTATION OF TEXTILE AGREEMENTS

Withdrawal of Calls on Categories 637 (Playsuits), 650 (Dressing Gowns), and 651 (Nightwear) From Hong Kong

January 17, 1985.

On May 10, June 7, and June 28, 1984 notices were published in the **Federal Register** (49 FR 19886, 23682 and 26623) announcing that on May 1, May 24 and June 7, 1984, the Government of the United States had requested the Government of Hong Kong to enter into consultations concerning exports to the United States of textile products in Categories 651, 650, and 637, produced or manufactured in Hong Kong. The purpose of this notice is to announce that the United States Government has concluded there is no need to establish limits for textile products in these categories at this time. Should it become necessary to discuss them with the Government of Hong Kong at a later date, further notice will be published in the **Federal Register.**

Walter C. Lenahan,

Chairman, Committee for the Implementation of Textile Agreements.

[FR Doc. 85–1698 Filed 1–22–85; 8:45 am]

BILLING CODE 3510–DR–M

DEPARTMENT OF DEFENSE

Department of the Army

M55 Rocket Stockpile Assessment Plan; Finding of No Significant Impact

AGENCY: Department of the Army, Department of Defense.

ACTION: Finding of No Significant Impact (FNSI) for the M55 Rocket Stockpile Assessment Plan. A comprehensive Environmental Assessment (EA) has been prepared which discusses the sampling operation to be used for characterizing the condition of the

rocket components (agent, propellant, metal, explosive burster, and fuze) through a programed composite of laboratory analyses. The test data derived from the analyses will be utilized to formulate important decisions regarding the ultimate disposition of the M55 rocket stockpile.

Sample collection will be conducted at six locations: Umatilla Depot Activity, Hermiston, Oregon; Tooele Army Depot, Tooele, Utah; Lexington-Blue Grass Depot Activity, Lexington, Kentucky; Pine Bluff Arsenal, Pine Bluff, Arkansas; Anniston Army Depot, Anniston, Alabama; and Johnston Island in the Central Pacific.

The assessment plan consists of several steps. First, the rocket motor, which contains no agent, will be removed from the warhead and shipped to Tooele Army Depot for further disassembly and analysis. Next, the chemical agent will be drained from the munitions into specially configured containers and placed in storage on site. Then, the agent and propellant samples and remaining rocket components will be shipped to several specialized analytical laboratories. Finally, all samples and components will be analyzed.

Shipments of the samples and components will be in full conformance with all applicable regulations (i.e., Federal, State, Army). The agent samples will be transported in specially designed containers via military air accompanied by US Army Technical Escort Unit personnel.

The proposed plan was selected after extensive study of several other options. Initially, the decision was made to conduct the rocket assessment instead of continuing the status quo of normal stockpile monitoring and surveillance procedures. Then, the proposed plan was selected over two other options: (a) Transporting the rockets to one location for disassembly, sampling and analysis; and (b) draining the rocket warheads prior to disassembly. The proposed plan appears to be optimum based on comparisons of safety, effectiveness, process simplicity, environmental impact and cost.

The Finding of No Significant Impact was established after consolidating site specific environmental assessments developed for each of the six sites. Because of safeguards built into the operation and contingency plans which have been developed for the extremely remote possibility of agent release and rocket detonation, no adverse environmental impact is associated with the M55 rocket assessment. Accordingly, an Environmental Impact Statement (EIS) is not required.

The complete Environmental Assessment, which includes all participating installations, is incorporated by reference and copies may be obtained from the Commander, Armament, Munitions and Chemical Command, ATTN: AMSMC–DS (M55 Functional Task Group), Rock Island, Illinois 61299.

Copies of the specific environmental documentation for each storage site may be obtained from the following locations:

Commander, Anniston Army Depot, ATTN: SDSAN–DAS–FE, Anniston, Alabama 26201

Commander, Lexington-Blue Grass Depot Activity, ATTN: SDSAN–LAF, Lexington, Kentucky 40507

Commander, Pine Bluff Arsenal, ATTN: SMCPB–EM, Pine Bluff, Arkansas 71601

Commander, Tooele Army Depot, ATTN: SDSTE–ASF–E, Tooele, Utah 84074

Commander, Umatilla Depot Activity, ATTN: SDSTE–UA–CO, Hermiston, Oregon 97838

Commander, WESTCOM, ATTN: APEN–ISF, Fort Shafter, Hawaii 96858.

Written public comments concerning this proposed action should be sent by February 22, 1985 to Commander, Armament, Munitions and Chemical Command, ATTN: AMSMC–DS (M55 Functional Task Group), Rock Island, Illinois 61299.

Lewis D. Walker,

Deputy for Environment, Safety and Occupational Health OASA(I&L).

[FR Doc. 85–1660 Filed 1–22–85; 8:45 am]

BILLING CODE 3710–08–M

Corps of Engineers; Department of the Army

Intent to Prepare an Environmental Impact Statement (EIS) to Address the Potential Cumulative Impacts of a Variety of Flood Plain Reclamation Projects Along the Trinity River and Its Tributaries in Tarrant and Dallas Counties, TX

AGENCY: U.S. Army Corps of Engineers, Fort Worth District, DOD.

ACTION: Notice of intent to prepare a Draft Environmental Impact Statement.

SUMMARY: 1. The main stem, West Fork, and Elm Fork, of the Trinity River in Dallas and Tarrant Counties, Texas, are currently proposed for extensive modification resulting from a series of individual flood plain reclamation project proposals subject to regulation by the Corps of Engineers under section 404 of the Clean Water Act and sections 9 and 10 of the River and Harbor Act of 1899. The principal purpose of the Draft Environmental Impact Study will be to address the potential cumulative impacts of these development on the river's hydrologic and hydraulic regimes.

2. Alternatives to be evaluated include flood plain development levels ranging from no further development to complete reclamation of the flood plain by private interests. Selection of the preferred alternative will be based on levels of development determined by the study to be compatible with the health and safety of downstream residents, as well as other study parameters, and will provide a framework within which to make decisions on individual permit actions.

3. The Draft EIS for the project will be circulated for review and comment by Federal, state, and local government entities, and by organizations and individuals known to have an interest in the project. Required coordination will be maintained with Federal, state, and local agencies during preparation of the document. Issues to be addressed will be "scoped" with these agencies and the public, and will include the effects of flood plain reclamation on regional flooding, water quality, solid waste disposal, transportation, recreation, aesthetics, archaeology, and fish and wildlife habitats as a minimum.

4. Scoping of issues will be conducted through scheduled meetings with representatives of affected local governments and appropriate state and Federal agencies in addition to a public scoping meeting planned for February 1985.

5. It is estimated that the Draft EIS will be available to the public in the first quarter of FY86.

ADDRESS: Questions about the proposed action may be addressed to: Ms. Rebecca Doby, Environmental Resources Branch, Fort Worth District, COE, P.O. Box 17300, Fort Worth, Texas 76102–0300. Telephone: 817/334–2095

Dated: January 14, 1985.

Stephenson W. Page,

Lieutenant Colonel, CE, Acting District Engineer.

[FR Doc. 85–1666 Filed 1–22–85; 8:45 am]

BILLING CODE 3710–20–M

DELAWARE RIVER BASIN COMMISSION

Commission Meeting and Public Hearing

Notice is hereby given that the Delaware River Basin Commission will

hold a public hearing on Wednesday, January 30, 1985, beginning at 1:30 p.m. in the Goddard Conference Room of the Commission's offices at 25 State Police Drive, West Trenton, New Jersey. The hearing will be a part of the Commission's regular business meeting which is open to the public.

An informal pre-meeting conference among the Commissioners and staff will be open for public observation at about 11:30 a.m. at the same location.

In addition to the hearing subjects listed below, please see the Proposed Rules section of today's issue of the **Federal Register** for details concerning the Commission's January 30, 1985 hearing on revised proposed amendments to the Commission's Ground Water Protected Area Regulations for Southeastern Pennsylvania.

Applications for Approval of the Following Projects Pursuant to Article 10.3, Article 11 and/or Section 3.8 of the Compact

1. *Holdover Project—New Jersey Water Company—Haddon District D–81–11 CP.* An amended application for a ground water withdrawal project to supply the applicant's Camden distribution system. New Well Nos. 53, 54 and 55 replace Well Nos. 46 through 49 which are no longer in use. Each of the three new wells is expected to yield 1.5 million gallons per day (mgd). However, the total withdrawal from existing and new wells will not be increased above the existing New Jersey Department of Environmental Protection limit of 193.75 million gallons (mg)/30 days. The new wells are located along Cleveland Avenue, between Reeves and 34th Streets, in the City of Camden, Camden County, New Jersey. This hearing continues that of December 12, 1984.

2. *Holdover Project—American Electric & Power Ltd. D–84–49.* A floating hydroelectric power generator in the Delaware River upstream of the City of Easton and between Forks Township, Northampton County, Pennsylvania and Lopatcong Township, Warren County, New Jersey. Up to 30 kilowatts of power will be produced by two parallel paddle wheels mounted on a 39 foot wide by 28 foot long pontoon boat. The vessel will be anchored to the river bottom using boat anchors but will be free to rise and fall with river stage except during low flow conditions, when it will rest on permanent support legs. It will be connected to the Pennsylvania shore only by a submarine cable connecting to the local electric transmission lines of Pennsylvania Power and Light Company. This hearing continues that of December 12, 1984.

3. *Borough of Hampton D–74–8 CP.* An application for a ground water withdrawal project to supply water to the applicant's distribution system located in Hampton and Glen Gardner Boroughs, Hunterdon County, New Jersey. Well No. 4 and standby Well Nos. 1 and 3, supply up to 6.6 mg/30 days to the distribution system.

4. *Perkasie Borough Authority D–79–28 CP RENEWAL.* Renewal of an approved ground water withdrawal from Well No. 10 which supplies water to the applicant's distribution system in Perkasie Borough and is projected to supply a small portion of East Rockhill Township in Bucks County, Pennsylvania. Commission approval was limited to five years and will expire unless renewed. The proposed 30-day withdrawal limit from Well No. 10 remains at 6.7 mg. The well is located in Perkasie Borough and in the Southeastern Pennsylvania Ground Water Protected Area.

5. *SPS Technologies, Inc. D–79–88 RENEWAL.* Renewal of an approved ground water withdrawal from Well No. 7 which supplies water to the applicant's manufacturing facility in the Borough of Jenkintown, Montgomery County, Pennsylvania. Commission approval was limited to five years and will expire unless renewed. The proposed 30-day withdrawal limit from Well No. 7 remains at 8.7 mg. The well is located in the Southeastern Pennsylvania Ground Water Protected Area.

6. *Borough of Downingtown D–84–43 CP.* A sewage treatment project to serve the Borough of Downingtown, and portions of Caln, East Caln, West Whiteland and Uwchlan Townships in Chester County, Pennsylvania. The plant will be upgraded and expanded to remove 96 percent BOD_5 (summer) and 88 percent suspended solids from an average waste flow of 7.0 million gallons per day (mgd). Treated effluent will discharge to the East Branch of Brandywine Creek in East Caln Township.

7. *Essex Industrial Chemicals D–84–85.* A ground water withdrawal project to provide for non-contact cooling at the applicant's hydrofluoric acid plant in the Borough of Paulsboro, Gloucester County, New Jersey. The applicant has abandoned and sealed an existing supply well, and has acquired two nearby existing wells from the Olin Corporation. Essex requests a total withdrawal from these wells (Nos. 1 and 2) of 34.6 mg per 30 days.

8. *Tenneco Polymers D–84–46.* A ground water withdrawal project to provide replacement sources of water to the applicant's manufacturing facility in Burlington Township, Burlington County, New Jersey. Existing Well Nos. 7, 8, and 9 were previously placed in service. The applicant does not request an increase in their present allocation of 114 mg per 30 days.

9. *Clement Pappas and Company D–84–48.* A ground water withdrawal project to serve the applicant's food processing facility in Upper Deerfield Township, Cumberland County, New Jersey. Water from the two existing wells will be used for cooling refrigeration condensers and domestic use. Well Nos. 6A and 7 have been purchased from Seabrook Foods Inc., and withdrawals from both wells were previously approved by Seabrook by Docket No. D–66–208. The applicant requests withdrawal rates of 43.2 mg/30 days from Well No. 6A, 30.2 mg/30 days from Well No. 7 and a total combined rate of 73.4 mg/30 days.

10. *Getty Refining and Marketing D–84–50.* A ground water withdrawal project to replace existing Well Nos. P–1, P–4 and P–10 which have supplied water since the mid-1950's to the applicant's oil refinery near Delaware City, New Castle County, Delaware. The applicant requests a combined withdrawal rate of 2.74 mgd from replacement Well Nos. P–1A, P–4A and P–10A. The applicant is not requesting an increase in their allocation of 180 mg/30 days from all wells.

11. *Standard Chlorine of Delaware D–84–51.* A ground water contaminant recovery and treatment system at the applicant's manufacturing facility near Delaware City, New Castle County, Delaware. The project is proposed to recover and treat ground water which has been contaminated through accidental spills of benzene compounds. Four recovery wells will withdraw ground water at a maximum total rate of 250 gallons per minute (0.36 mgd). Benzene compounds will be removed via a new air stripper-clarifier-filtration treatment facility which will discharge treated effluent to the Delaware River.

12. *Merchantville-Pennsauken Water Commission D–84–52 CP.* A ground water withdrawal project to provide a replacement source of water for the applicant's distribution system which serves the Borough of Merchantville and the Township of Pennsauken as well as portions of the City of Camden and Cherry Hill Township in Camden County, New Jersey. National Highway Well No. 2 replaces an existing well, Delaware Gardens Well No. 1A, which has been abandoned due to high manganese concentrations. The

applicant proposes to withdraw 30 mg/30 days from the new well, located in Pennsauken Township. This project also renews the approval granted by Docket No. D–79–10 CP which otherwise expires on February 25, 1985.

Documents relating to these items may be examined at the Commission's offices. Preliminary dockets are available in single copies upon request. Please contact David B. Everett. Persons wishing to testify at this hearing are requested to register with the Secretary prior to the hearing.

Susan M. Weisman,

Secretary.

January 14, 1985.

[FR Doc. 85–1672 Filed 1–22–85; 8:45 am]

BILLING CODE 6360–01–M

DEPARTMENT OF EDUCATION

Proposed Information Collection Requests

AGENCY: Department of Education.

ACTION: Notice of proposed information collection requests.

SUMMARY: The Deputy Under Secretary for Management invites comments on the proposed information collection requests as required by the Paperwork Reduction Act of 1980.

DATES: Interested persons are invited to submit comments on or before February 22, 1985.

ADDRESSES: Written comments should be addressed to the Office of Information and Regulatory Affairs, Attention: Desk Officer, Department of Education, Office of Management and Budget, 726 Jackson Place, NW., Room 3208, New Executive Office Building, Washington, D.C. 20503. Requests for copies of the proposed information collection requests should be addressed to Margaret B. Webster, Department of Education, 400 Maryland Avenue, SW., Room 4074, Switzer Building, Washington, D.C. 20202.

FOR FURTHER INFORMATION CONTACT: Margaret B. Webster (202) 426–7304.

SUPPLEMENTARY INFORMATION: Section 3517 of the Paperwork Reduction Act of 1980 (44 U.S.C. Chapter 35) requires that the Office of Management and Budget (OMB) provide interested Federal agencies and the public an early opportunity to comment on information collection requests. OMB may amend or waive the requirement for public consultation to the extent that public participation in the approval process would defeat the purpose of the information collection, violate State or Federal law, or substantially interfere with any agency's ability to perform its statutory obligations.

The Deputy Under Secretary for Management publishes this notice containing proposed information collect requests prior to the submission of these requests to OMB. Each proposed information collection, grouped by office, contains the following: (1) Type of review requested, e.g., new, revision, extension, existing or reinstatement; (2) Title; (3) Agency form number (if any); (4) Frequency of the collection; (5) The affected public; (6) Reporting burden; and/or (7) Recordkeeping burden; and (8) Abstract.

OMB invites public comment at the address specified above. Copies of the requests are available from Margaret Webster at the address specified above.

Dated: January 16, 1985.

Linda M. Combs,

Deputy Under Secretary for Management.

Office of Elementary and Secondary Education

Type of Review Requested: Extension
Title: Section 554 of the Education Consolidation and Improvement Act of 1981; Application for Federal Assistance under Section 141 of Title I of the Elementary and Secondary Education Act of 1965, as amended: The Migrant Education Basic State Formula Grant Program
Agency Form Number: ED 362
Frequency: Annually
Affect Public: State Governments
Reporting Burden: Responses: 51; Burden Hours: 408
Recordkeeping Burden: Recordkeepers: 51; Burden Hours: 408

Abstract: Chapter 1, ECIA, Migrant Education Program requires the submission of a State Migrant Education Program Application for an annual program grant. The Department of Education Division of Migrant Education conducts a comprehensive application review and approval process prior to awarding a grant to each State.

[FR Doc. 85–1703 Filed 1–22–85; 8:45 am]

BILLING CODE 4000–01–M

Nurse Education; Accrediting Bodies and State Approval Agencies

AGENCY: Department of Education.

ACTION: Notice; List of Accrediting Bodies and State Approval Agencies Recognized for the Approval of Nurse Education.

SUMMARY: The Secretary of Education lists accrediting bodies and State approval agencies that he determines to be reliable authorities on the quality of training offered by schools and programs for diplomas, associate degrees, baccalaureate degrees and graduate degrees in nursing. The Secretary publishes this list for institutional eligibility purposes under the Nurse Training Act, as amended.

FOR FURTHER INFORMATION CONTACT: Joan Givens, Agency Evaluation Branch, Division of Eligibility and Agency Evaluation, Office of Postsecondary Education, 400 Maryland Avenue, SW. (Room 3637, ROB–3), U.S. Department of Education, Washington, D.C. 20202.

SUPPLEMENTARY INFORMATION: For the purpose of determining institutional eligibility for Federal assistance under the Nurse Training Act, as amended, which is administered by the Department of Health and Human Services, the Secretary of Education is required to publish a list or recognized accrediting bodies and State agencies that he determines to be reliable authorities on the quality of training offered by schools and programs for diplomas, associate degrees, baccalaureate degrees and graduate degrees in nursing (42 U.S.C. 298b(6)). The most recent list was published in the **Federal Register** on January 19, 1979, 44 FR 4020. This list supersedes that list.

Accrediting and State Approval Agencies Recognized for the Approval of Nurse Education

Regional Institutional Accrediting Associations

New England Association of Schools and Colleges
- Commission on Institutions of Higher Education
- Commission on Vocational, Technical, and Career Institutions

Regional Institutional Accrediting Commissions

Accrediting Commission for Community and Junior Colleges, Western Association of Schools and Colleges
Accrediting Commission for Senior Colleges and Universities, Western Association of Schools and Colleges
Commission of Colleges, Northwest Association of Schools and Colleges
Commission on Colleges, Southern Association of Colleges and Schools
Commission on Higher Education, Middle States Association of Colleges and Schools
Commission on Institutions of Higher Education, North Central Association of Colleges and Schools

National Specialized Accrediting Agencies and Associations

National League for Nursing, Inc.

Board of Review for Associate Degree Programs
Board of Review for Baccalaureate and Higher Degree Programs
Board of Review for Diploma Programs

State Agencies

Iowa Board of Nursing
Louisiana State Board of Nursing
Missouri State Board of Nursing
Montana Board of Nursing
New Hampshire Board of Nursing Education and Nurse Registration
New York State Board of Regents (Nursing Education Unit)
West Virginia Board of Examiners for Registered Nurses

Agencies Withdrawn From List

California Board of Registered Nursing (at its request)

(42 U.S.C. 298b(6))

(Catalog of Federal Domestic Assistance Number not applicable)

Dated: January 17, 1985.

Gary L. Jones,

Acting Secretary of Education.

[FR Doc. 85-1701 Filed 1-22-85; 8:45 am]

BILLING CODE 4000-01-M

Office of Postsecondary Education

Law School Clinical Experience Program; Application Notice for New Awards for Fiscal Year 1985

This notice invites applications for new awards under the Law School Clinical Experience Program.

Authority for this program is contained in Part E of Title IX, of the Higher Education Act of 1965, as amended by Pub. L. 98-312.

(20 U.S.C. 1134n-1134p)

This program issues awards to accredited law schools, or combinations or consortiums of accredited law schools.

The purpose of the Law School Clinical Experience Program is to establish or expand projects at accredited law schools to provide supervised clinical experience to students in the practice of law.

Closing date for transmittal of applications: An application for an award must be mailed or hand-delivered by March 25, 1985.

Applications delivered by mail: An application sent by mail must be addressed to the U.S. Department of Education, Application Control Center, Attention: 84.097, Washington, D.C. 20202.

An applicant must show proof of mailing consisting of one of the following:

(1) A legibly dated U.S. Postal Service postmark.

(2) A legible mail receipt with the date of mailing stamped by the U.S. Postal Service.

(3) A dated shipping label, invoice, or receipt from a commercial carrier.

(4) Any other proof of mailing acceptable to the U.S. Secretary of Education.

If an application is sent through the U.S. Postal Service, the Secretary does not accept either of the following as proof of mailing: (1) A private metered postmark, or (2) a mail receipt that is not dated by the U.S. Postal Service.

An applicant should note that the U.S. Postal Service does not uniformly provide a dated postmark. Before relying on this method, an applicant should check with its local post office.

An applicant is encouraged to use registered or at least first class mail. Each late applicant will be notified that its application will not be considered.

Applications delivered by hand: An application that is hand-delivered must be taken to the U.S. Department of Education, Application Control Center, Room 5673 Regional Office Building 3, 7th and D Streets, SW., Washington, D.C.

The Application Control Center will accept a hand-delivered application between 8:00 a.m. and 4:30 p.m. (Washington, D.C. time), daily except Saturdays, Sundays, and Federal holidays.

An application that is hand-delivered will not be accepted after 4:30 pm. on the closing date.

Program Information

Eligible applicants: Only accredited law schools or combinations or consortiums of accredited law schools may apply for awards.

(20 U.S.C. 134n(d))

Available funds: The Department of Education Appropriation Act, 1985, appropriated $1,500,000 for the Law School Clinical Experience Program.

The program legislation permits the Secretary to pay up to 90 percent of the costs of projects at law schools. The program regulations permit the Secretary to establish annually a lower maximum Federal share. In Fiscal Year 1984, with a $1 million appropriation, the maximum Federal share was 50 percent. With a funding level of $1,500,000 for Fiscal Year 1985, the Secretary is once again establishing a maximum Federal share of 50 percent. A major objective of this program is to increase the financial commitment of a law school to clinical legal education. Support of clinical legal education is not a permanent Federal responsibility. The setting of the Federal share at 50 percent supports the program's objective. The Secretary expects to make about 40 or 50 awards, averaging approximately $30,000.

These estimates do not bind the Department of Education to a specific number of grants or to the amount of any grant unless that amount is otherwise specified by statute or regulations.

Final regulations governing the Law School Clinical Experience Program were published in the **Federal Register** on July 14, 1981. These regulations broadly defined the types of projects the Secretary intends to support under this program. The regulations also specify the selection criteria to be used in evaluating applications.

Application forms: Application forms and program information packages are expected to be ready for mailing by January 25, 1985, and may be obtained by writing to the Division of Higher Education Incentive Programs (Law School Clinical Experience Program), U.S. Department of Education (Room 3022, Regional Office Building 3), 400 Maryland Avenue, SW., Washington, D.C. 20202. (Approved Under OMB No. 1840-0041.)

Applications must be prepared and submitted in accordance with the regulations, funding criteria, instructions, and forms included in the program information package.

The program information package is intended to aid applicants applying for a grant under this competition. Nothing in the program information package is intended to impose any paperwork, application content, reporting or grantee performance requirement beyond those specifically imposed under the statute and regulations governing the competition.

Applicable regulations: The regulations applicable to this program include the following:

(1) The Education Department General Administrative Regulations (EDGAR) in 34 CFR Parts 74, 75, 77, and 78.

(2) The regulations governing the Law School Clinical Experience Program, in 34 CFR Part 639.

Further information: For further information contact Division of Higher Education Incentive Programs (Law School Clinical Experience Program), U.S. Department of Education (Room 3022, Regional Office Building 3), 400 Maryland Avenue, SW., Washington, D.C. 20202, Telephone: (202) 245-2511.

(20 U.S.C. 1134n-1134p)

(Catalog of Federal Domestic Assistance Number 84.097, Law School Clinical Expereince Program)

Dated: January 17, 1985.

Gary L. Jones,

Acting Secretary of Education.

[FR Doc. 85–1702 Filed 1–22–85; 8:45 am]

BILLING CODE 4000–01–M

Office of Special Education and Rehabilitative Services

The State Vocational Rehabilitation Services Program

AGENCY: Department of Education.

ACTION: Notice of waiver.

SUMMARY: The Secretary waives the requirement that the Department of Education give prior approval for certain categories of costs under the Basic State Vocational Rehabilitation Grant program authorized by Title I of the Rehabilitation Act of 1973, as amended.

EFFECTIVE DATE: This waiver is effective January 23, 1985.

FOR FURTHER INFORMATION CONTACT: Mark E. Shoob, Chief, Basic State Grants Branch, Rehabilitation Services Administration, Room 3211 Switzer Building, 330 C Street, SW., Washington, D.C. 20202, (202) 732–1402.

SUPPLEMENTARY INFORMATION: The Education Department General Administrative Regulations (EDGAR), at 34 CFR 74.176, require that grantees obtain prior approval of the Department before using grant funds for various categories of costs. For grants to State and local governments, such as those made to State vocational rehabilitation agencies under the Basic State Vocational Rehabilitation Grant program authorized by Title I of the Rehabilitation Act of 1973 as amended (29 U.S.C. 720 *et seq.*), those cost categories are listed in EDGAR Part 74, Appendix C, Part II–C. The Secretary believes that it is no longer necessary to require prior approval with respect to four of the eight cost categories listed in that Appendix. Those four categories are: (1) Building space and related facilities, except for rearrangements and alterations that materially increase the value or useful life of facilities and thus are regarded as capital expenditures; (2) insurance and indemnification; (3) preagreement costs; and (4) proposal costs. The Secretary has rarely declined to approve requests for prior approval for these categories, does not believe that grantees will inappropriately use grant funds for these categories if the requirement for prior approval is waived, and believes that grantees should be relieved of the paperwork burden of requesting prior approval under these categories. Under the authority of 34 CFR 74.176(c), the Secretary therefore waives the requirement of prior approval with respect to the four cost categories listed above.

The Secretary also notes that this waiver applies only to the requirement to obtain prior approval from the Department. If, upon audit or otherwise, it is determined that the claimed expenditures do not meet other requirements or tests for allowability specified by the applicable cost principles, such as reasonableness and necessity, the costs may be disallowed. With respect to insurance and indemnification, for example, the applicable cost principles set out various limitations and requirements which continue to apply. See 34 CFR Part 74, Appendix C, Part II.C.4.

The four remaining cost categories requiring prior approval are: (1) Automatic data processing; (2) capital expenditures; (3) management studies; and (4) professional services. The Rehabilitation Services Administration (RSA), which administers the Title I program, has found that it can provide significant guidance to States seeking to use program funds for those costs. For example, in the area of automatic data processing, RSA has frequently responded to requests for prior approval with technical advice that has assisted grantees to save money or better meet their automatic data processing needs. Similarly, RSA has often referred States to relevant management studies that have already been completed, thereby reducing or eliminating the need for additional studies. Based on this program experience and the concern that program funds not be unnecessarily diverted from the direct provision of services, the Secretary will continue to require that grantees obtain the Department's approval before using program funds for these cost categories.

(29 U.S.C. 720 et seq.; 34 CFR 74.176(c))

Dated: January 17, 1985.

Gary L. Jones,

Acting Secretary of Education.

[FR Doc. 85–1704 Filed 1–22–85; 8:45 am]

BILLING CODE 4000–01–M

DEPARTMENT OF ENERGY

Office of Energy Research

Energy Research Advisory Board; Open Meeting

Pursuant to the provisions of the Federal Advisory Committee Act (Pub. L. 92–463, 86 Stat. 770), notice is hereby given of the following meeting:

Name: Energy Research Advisory Board (ERAB)

Date and Time:

February 7, 1985 from 8:30 a.m. to 5 p.m.
February 8, 1985 from 8:30 a.m. to 3 p.m.

Place: U.S. Department of Energy, 1000 Independence Avenue, SW., Room 8–E089, Washington, DC 20585.

Contact: Sarah Goldman, U.S. Department of Energy, Office of Energy Research, 1000 Independence Avenue, SW., Washington, DC 20585, (202) 252–5444

Purpose of the parent board: To advise the Department of Energy (DOE) on the overall research and development conducted in DOE and to provide long-range guidance in these areas to the Department.

Tentative agenda: The specific agenda items and times are frequently subject to last minute changes. Visitors planning to attend for a specific topic should confirm the time prior to and during the day of the meeting.

Draft Agenda

February 7

8:30 a.m.
—Administrative Items
—Approval of Minutes
—Schedule of Future Meetings
9:00 a.m. National Laboratory Views on Long Range Energy R&D Strategy
10:45 a.m. Roundtable Discussion with Laboratory Directors
12:00 Noon Lunch
1:00 p.m. Long Range Energy R&D Strategy Study Overview/Report from Steering Committee
1:30 p.m. Infrastructure Subpanel Status
2:00 p.m. Supply Subpanel Status
2:45 p.m. Demand Subpanel Status
3:15 p.m. Research Subpanel Status
3:45 p.m. Discussion of Next Steps. Crosscutting Issues
5:00 p.m. Public Comment (10 minute rule)/ Adjourn

February 8

8:30 a.m. Light Water Reactor Panel Report
9:45 a.m. Clean Coal Panel Status
10:45 a.m. Materials Facilities Panel Status
11:30 a.m. International Panel Status
12:00 noon Lunch
1:00 p.m. Briefing on DOE FY 1986 Proposed Budget
2:00 p.m. Current R&D Issues:
—Patent Changes
—FY 1986 Budget Implication
—Selection Process, Superconducting Super Collider
2:50 p.m. Public Comment (10 minute rule)
3:00 p.m. Adjourn

Public Participation

The meeting is open to the public. Written statements may be filed with the Board either before or after the

meeting. Members of the public who wish to make oral statements pertaining to agenda items should contact Sarah Goldman at the address or telephone number listed above. Requests must be received 5 days prior to the meeting and reasonable provisions will be made to include the presentation on the agenda. The Chairperson of the Board is empowered to conduct the meeting in a fashion that will facilitate the orderly conduct of business.

Transcripts

Available for public review and copying at the Freedom of Information Public Reading Room, Forrestal Building, 1000 Independence Avenue, SW, Washington, DC between 9 a.m. and 4 p.m., Monday through Friday, except Federal holidays.

Issued at Washington, DC on January 16, 1985.

Howard H. Raiken,

Deputy Advisory Committee Management Officer.

[FR Doc. 85-1678 Filed 1-22-85; 8:45 am]

BILLING CODE 6450-01-M

Energy Research Advisory Board Demand Subpanel of the Energy R&D Strategy Panel; Meeting Change

This notice is to advise of the new times for the meeting of the Energy Research Advisory Board (ERAB) Demand Subpanel of the Energy R&D Strategy Panel (February 6, 1985) as published in the issue of December 18, 1984 (FR 49168).

The ERAB Demand Subpanel will hold its meeting starting at 1:00 p.m. and adjouring at 4:30 p.m. The agenda topics will remain the same. The meeting will be held at the U.S. Department of Energy, 1000 Independence Avenue, SW., Room 6A-110, Washington, DC 20585.

Issued at Washington, DC on January 16, 1985.

Charles E. Cathey,

Deputy Director, Office of Science and Technology Affairs, Office of Energy Research.

[FR Doc. 85-1735 Filed 1-22-85; 8:45 am]

BILLING CODE 6450-01-M

Energy Research Advisory Board Supply Subpanel of the Energy R&D Strategy Panel; Meeting Change

This notice is to advise of the new date and times of the meeting of the Energy Research Advisory Board (ERAB) Supply Subpanel of the Energy R&D Strategy Panel (February 6, 1985) as published in the issue of December 18, 1984 (49 FR 49169).

The ERAB Supply Subpanel will hold its meeting starting at 10:00 a.m. and adjourning at 4:30 p.m., on February 5, 1985. The agenda will remain the same. The meeting will be held at the U.S. Department of Energy, 1000 Independence Avenue, SW., Room 4A-110, Washington, DC 20585.

Issued at Washington, DC on January 8, 1985.

Charles E. Cathey,

Deputy Director, Office of Science & Technology Affairs, Office of Energy Research.

[FR Doc. 85-1736 Filed 1-22-85; 8:45 am]

BILLING CODE 6450-01-M

High Energy Physics Advisory Panel; Open Meeting

Pursuant to the provisions of the Federal Advisory Committee Act (Pub. L. 92-463, 86 Stat. 770), notice is hereby given of the following meeting:

Meeting: High Energy Physics Advisory Panel (HEPAP).

Date and time: Monday, February 11, 1985, 9 a.m. to 6 p.m., Tuesday, February 12, 1985, 9 a.m. to 5 p.m.

Place: U.S. Department of Energy, Room A410, 19901 Germantown Road, Germantown, MD 20874.

Contact: Dr. P. K. Williams, Executive Secretary, High Energy Physics Advisory Panel, U.S. Department of Energy, ER-221, Washington, DC 20545, Telephone: 301-353-4829.

Purpose of panel: To provide advice and guidance on a continuing basis with respect to the high energy physics research program.

Tentative Agenda

Monday, February 11, 1985

—Discussion of Department of Energy/High Energy Physics and National Science Foundation/Elementary Particle Physics FY 1986 President's Budget Request, if available
—Discussion of status of Superconducting Super Collider (SSC) R&D activities
—Discussion of long range planning and the HEPAP 1985 Summer Study

Tuesday, February 12, 1985

—Status of Standford Linear Collider (SLC) construction and Positron-Electron Project (PEP) upgrade plans at Stanford Linear Accelerator Center
—Status of Tevatron I construction and Tevatron II construction and operations at Fermi National Accelerator Laboratory
—Status of Cornell Electron Storage Ring (CESR) upgrade
—Report on progress at the Large Electron-Positron Facility (LEP) at the European Organization for Nuclear Research (CERN)
—Report on meeting of International Committee on Future Accelerators (ICFA)
—Further discussion on planning for HEPAP 1985 Summer Study
—Public Comment (10 minute rule)

Public Participation

The meeting is open to the public. The Chairperson of the Panel is empowered to conduct the meeting in a fashion that will, in his judgment, facilitate the orderly conduct of business. Any member of the public who wishes to make oral statements pertaining to agenda items should contact the Executive Secretary at the address or telephone number listed above. Requests must be received at least five days prior to the meeting and reasonable provision will be made to include the presentation on the agenda.

Minutes

Available for public review and copying at the Public Reading Room, Room 1E-190, Forrestal Building, 1000 Independence Avenue, SW., Washington, DC between 9 a.m. and 4 p.m. Monday through Friday, except Federal Holidays.

Issued at Washington, DC on January 17, 1985.

Howard H. Raiken,

Deputy Advisory Committee, Management Officer.

[FR Doc. 85-1732 Filed 1-22-85; 8:45 am]

BILLING CODE 6450-01-M

National Petroleum Council Refinery Survey Task Group; Date/Location Change for Meeting

The date and location of the January 17, 1985, meeting of the Refinery Survey Task Group, which was to be held at the Conference Room of the National Petroleum Council, 1625 K Street, NW, Suite 600, Washington, D.C., has been changed. The new date and location should read: Tuesday, January 29, 1985, starting at 9:00 a.m., in the Conference Room of the National Petroleum Council, 1625 K Street, NW, Suite 600, Washington, D.C.

Issued at Washington, D.C., January 11, 1985.

William A. Vaughan,

Assistance Secretary, Fossil Energy.

[FR Doc. 85-1733 Filed 1-22-85; 8:45 am]

BILLING CODE 6450-01-M

Federal Energy Regulatory Commission

[Docket No. ER85-218-000]

Boston Edison Co.; Filing

January 15, 1985.

The filing Company submits the following:

Take notice that on January 4, 1985, Boston Edison Company (Edison) tendered for filing an agreement for the exchange of power between itself and Cambridge Electric Light Company of Wareham, Massachusetts (Cambridge).

Under the agreement, the parties could negotiate daily power exchanges involving Edison fossil fired units and Cambridge fossil fired facilities. The parties state that the purpose of the power exchanges is to attain greater efficiencies of operation.

Copies of the filing have been served upon Cambridge and on the Department of Public Utilities of the Commonwealth of Massachusetts.

Any person desiring to be heard or to protest said filing should file a motion to intervene or protest with the Federal Energy Regulatory Commission, 825 North Capitol Street, NE, Washington, D.C. 20426, in accordance with Rules 211 and 214 of the Commission's Rules of Practice and Procedure (18 CFR 385.211, 385.214). All such petitions or protests should be filed on or before January 29, 1985. Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make protestants parties to the proceeding. Any person wishing to become a party must file a petition to intervene. Copies of this filing are on file with the Commission and are available for public inspection.

Kenneth F. Plumb,

Secretary.

[FR Doc. 85-1644 Filed 1-22-85; 8:45 am]

BILLING CODE 6717-01-M

[Docket No. ER85-219-000]

Southern California Edison Co.; Cancellation

January 15, 1985.

Take notice that on January 7, 1985, Southern California Edison Company (Edison) tendered for filing a Notice of Cancellation Rate Schedule FPC No. 150.

Edison states that this agreement includes a contractual agreement, executed on January 7, 1982, between Edison and the City of Burbank, California for the delivery of hydroelectric energy purchased by Burbank from the Metropolitan Water District of Southern California to the City of Pasadena for the City of Burbank's account.

Edison requests an effective date of January 4, 1984, and therefore requests waiver of the Commission's notice requirements.

Copies of this filing have been served on the City of Burbank.

Any person desiring to be heard or to protest said filing should file a motion to intervene or protest with the Federal Energy Regulatory Commission, 825 North Capitol Street, NE., Washington, D.C. 20426, in accordance with Rules 211 and 214 of the Commission's Rules of Practice and Procedure (18 CFR 385.211, 385.214). All such motions or protests should be filed on or before January 29, 1985. Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make protestants parties to the proceeding. Any person wishing to become a party must file a motion to intervene. Copies of this filing are on file with the Commission and are available for public inspection.

Kenneth F. Plumb,

Secretary.

[FR Doc. 85-1645 Filed 1-22-85; 8:45 am]

BILLING CODE 6717-01-M

[Project No. 6752-001, et al.]

Hydroelectric Applications (New Hampshire Water Resources Board, et al.); Applications Filed With the Commission

Take notice that the following hydroelectric applications have been filed with the Federal Energy Regulatory Commission and are available for public inspection:

1 a. Type of Application: Exemption (5 MW or Less).

b. Project No.: 6752-001.

c. Date Filed: September 27, 1984.

d. Applicant: New Hampshire Water Resources Board.

e. Name of Project: Avery Dam.

f. Location: On the Winnipesaukee River in Belknap County, New Hampshire.

g. Filed Pursuant to: Energy Security Act of 1980, Section 408, 16 U.S.C. 2705 and 2708 *as amended.*

h. Contact Person: Morris J. Root, Dufresne-Henry, Inc., Precision Park, North Springfield, Vermont 05150.

i. Comment Date: February 25, 1985.

j. Description of Project: The proposed run-of-river project would consist of: (1) The existing 20.5-foot-high and 114-foot-long concrete Avery Dam owned by the Applicant with a spillway crest elevation of 491.5 feet mean sea level; (2) a reservoir (Opechee Bay) with a surface area of 455 acres and a gross storage capacity of 3,700 acre-feet; (3) a new 25-foot-long headrace canal; (4) two new submergible turbine-generator units within the downstream end of the canal with a total installed capacity of 192 kW; (5) a short tailrace; (6) a 150-foot-long transmission line; and (7) other appurtenances. Applicant estimates an average annual generation of 950,000 kWh. The application was filed during the Applicant's preliminary permit term for Project No. 6752.

k. Purpose of Project: Project energy would be sold to the Public Service Company of New Hampshire.

l. This notice also consists of the following standard paragraphs: A1, A9, B, C, and D3a.

m. Purpose of Exemption: An exemption, if issued, gives the Exemptee priority of control, development, and operation of the projects under the terms of the exemption from licensing, and protects the Exemptee from permit or license applicants that would seek to take or develop the project.

2. a. Type of Application: Preliminary Permit.

b. Project No: 8374-001.

c. Date Filed: October 29, 1984.

d. Applicant: R&D Power Company.

e. Name of Project: Northern California No. 1 Power Project.

f. Location: On Eagle Creek, near Trinity Center, within Shasta National Forest, in Trinity County, California.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)-825(r).

h. Contact Person: Mr. William Dean Coldiron, Jr., P.O. Box 4254, Mountain View, California 94040.

i. Comment Date: March 15, 1985.

j. Description of Project: The proposed project would consist of: (1) A 4-foot-high, 40-foot-long diversion dam at elevation 3,630 feet; (2) a 24-inch-diameter, 2,000-foot-long steel penstock; (3) a powerhouse with a total installed capacity of 610 kW operating under a head of 320 feet; and (4) a 15,000-foot-long, 12-kV transmission line from the powerhouse to connect to an existing 12-kV Pacific Gas and Electric Company (PG&E) transmission line. The Applicant estimates the average annual energy generation at 2.84 million kWh to be sold to PG&E.

A preliminary permit, if issued, does not authorize construction. The Applicant seeks issuance of a 36-month preliminary permit to conduct technical, environmental and economic studies, and also prepare an FERC license application at an estimated cost of $25,000.

k. This notice also consists of the following standard paragraphs: A6, A7, A9, B, C, and D2.

3. a. Type of Application: Preliminary Permit.

b. Project No: 8692–000.

c. Date Filed: October 30, 1984.

d. Applicant: Union Village Hydroelectric Company.

e. Name of Project: Covered Bridge.

f. Location: On the Ompompanoosuc River in Orange County, Vermont.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: John L. Warshow, Union Village Hydroelectric Company, 26 State Street, Montpelier Vermont 05602.

i. Comment Date: March 11, 1985.

j. Description of Project: The proposed project will utilize the existing U.S. Army Corps of Engineers' Covered Bridge Dam and consist of: (1) A proposed 4-foot-diameter, 350-foot-long penstock; (2) a proposed powerhouse which will contain an installed generating capacity of 300 kW; (3) a proposed 1,500-foot-long, 7.2-kV transmission line; and (4) appurtenant facilities. The Applicant estimates the average annual energy generation to be approximately 1.0 GWh. It is anticipated that the power will be sold either to the interconnecting utility or to the Vermont Power Exchange.

k. This notice also consists of the following standard paragraphs: A5, A7, A9, B, C, and D2.

l. Proposed Scope of Studies Under Permit: A preliminary permit, if issued, does not authorize construction. The term of the proposed preliminary permit is 18 months. The works proposed under the preliminary permit would include economic analysis, preparation of preliminary engineering plans, and a study of environmental impacts. Based on results of these studies, Applicant would decide whether to proceed with more detailed studies, and the preparation of an application for license to construct and operate the project. Applicant estimates that the cost of the work to be performed under the preliminary permit would be $50,000.

4 a. Type of Application: Preliminary Permit.

b. Project No: 8682–000.

c. Date Filed: October 22, 1984.

d. Applicant: City of Colonial Heights, Virginia.

e. Name of Project: Lakeview Dam Hydro.

f. Location: On Swift Creek in Chesterfield County, Virginia.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Robert V. Cawthorne, City of Colonial Heights, P.O. Box 248, Colonial Heights, Virginia 23834.

i. Comment Date: March 11, 1985.

j. Description of Project: The proposed project would consist of: (1) An existing concrete dam with total length of approxiately 420 feet and maximum height of about 39 feet; (2) an existing reservoir with a storage capacity of about 940 acre-feet and a water surface area of 93 acres at elevation 60.6 feet, m.s.l.; (3) a new steel penstock 7 feet in diameter and 10 feet long; (4) a new concrete powerhouse, 34 feet by 15 feet, housing one turbine-generator with an installed capacity of 600 kW; (5) a proposed 13,200-volt transmission line approximately 400 feet in length; and (6) appurtenant facilities. Applicant estimates that the average annual energy generation would be 1,720,000 kWh. The dam is owned by the City of Colonial Heights.

k. Purpose of Project: The Applicant anticipates that project energy will be sold to the Virginia Electric Power Company.

l. This notice also consists of the following standard paragraphs: A5, A7, A9, B, C, and D2.

m. Proposed Scope of Studies under Permit: A preliminary permit, if issued, does not authorize construction. Applicant seeks issuance of a preliminary permit for a period of 36 months during which time it would prepare studies of the hydraulic, construction, economic, environmental, historic and recreational aspects of the project. Depending on the outcome of the studies, Applicant would prepare an application for an FERC license. Applicant estimates the cost of the studies under the permit would be $30,000.

5 a. Type of Application: Preliminary Permit.

b. Project No: 8775–000.

c. Date Filed: December 5, 1984.

d. Applicant: DeSoto Hydro Associates.

e. Name of Project: DeSoto Park Dam Hydro Project.

f. Location: On the West Fork of the Little River near Valley Head, DeKalb County, Alabama.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Mr. Casey A. Cummings, Synergics, Inc., 410 Severn Avenue, Suite 409, Annapolis, Maryland 21403.

i. Comment Date: March 6, 1985.

j. Description of Project: The proposed project would consist of: (1) An existing 20-foot-high and 217-foot-long concrete dam; (2) an existing reservoir with a gross storage capacity of approximately 20 acre-feet at normal water surface elevation of 1630.8 feet m.s.l.; (3) a proposed 4-foot-diameter steel penstock approximately 440 feet long; (4) a new 23 feet wide by 18 feet long powerhouse with a single generator having a rated capacity of 700 kW; (5) a new 112.5-kV transmission line that will interconnent with Alabama Power Company's transmission system; and (6) appurtenant facilities. The Applicant estimates the average annual generation would be 2,000 MWh. The existing project dam is owned by the State of Alabama. All project energy generated would be sold to Alabama Power Company.

k. This notice also consists of the following standard paragraphs A5, A7, A9, B, C, & D2.

l. Proposed Scope of Studies under Permit: A preliminary permit, if issued, does not authorize construction. Applicant seeks issuance of a preliminary permit for a period of 18 months during which time Applicant would investigate project design alternatives, financial feasibility, environmental effects of project construction and operation, and project power potential. Depending upon the outcome of the studies, the Applicant would decide whether to proceed with an application for FERC license. Applicant estimates that the cost of the studies under permit would be $60,000.

6 a. Type of Application: Preliminary Permit.

b. Project No: 8759–000.

c. Date Filed: December 3, 1984.

d. Applicant: County of Amador.

e. Name of Project: Devils Nose Hydro.

f. Location: On the North Fork Mokelumne River within Eldorado National Forest in Amador and Calaveras Counties, California.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Kenneth Deaver, Chairman, Board of Supervisors, County of Amador, 108 Court Street, Jackson, California 95642.

i. Comment Date: March 8, 1985.

j. Description of Project: The proposed project would consist of: (1) A 400-foot-high earthfill dam at elevation 2,980 feet; (2) a reservoir with gross storage capacity of 103,000 acre-feet; (3) a 13,800-foot-long tunnel; (4) a 900-foot-long penstock; (5) a powerhouse containing three generating units with combined installed capacity of 30,600 kW operating under a head of 545 feet; and (6) a 230-kV, 1-mile-long transmission line would connect the project with an existing Pacific Gas and Electric Company (PG&E) transmission line north of the powerhouse.

k. Purpose of Project: The estimated annual generation of 90 million kWh would be sold to PG&E.

l. This notice also consists of the following standard paragraphs: A6, A7, A9, B, C & D2.

7 a. Type of Application: Preliminary Permit.

b. Project No: 8690–000.

c. Date Filed: October 29, 1984.

d. Applicant: Coralville Hydro Associates.

e. Name of Project: Coralville Dam.

f. Location: In Johnson County, on the Iowa River.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Philip M. Hoover, Synergics, Incorporated, 410 Severn Avenue, Suite 409, Annapolis, Maryland 21403.

i. Comment Date: March 6, 1985.

j. Competing Application: Project No. 8691–000, Date Filed: October 29, 1984.

k. Description of Project: The proposed project would consist of: (1) A 14-foot-high and 295-foot-long existing dam including spillway owned by the Johnson County Conservation Board; (2) a reservoir of negligible size and storage capacity; (3) a proposed power canal 75 feet long and 30 feet wide; (4) a proposed concrete powerhouse 25 feet long and 30 feet wide containing two proposed turbine/generators with a total rated capacity of 1800 kW; (5) a proposed tailrace 25 feet long and 25 feet wide; (6) a new transmission line; and (7) appurtenant facilities. The estimated average annual energy produced by the project would be 8,500,000 kWh operating under a net hydraulic head of 14 feet. Project power would be sold to the Iowa Electric Light and Power Company.

l. This notice also consists of the following standard paragraphs: A5, A7, A9, B, C, D2.

m. Proposed Scope of Studies under Permit: A preliminary permit, if issued, does not authorize construction. The term of the proposed preliminary permit is 18 months. The work proposed under the preliminary permit would include economic analysis, preparation of preliminary engineering plans, and a study of environmental impacts. Based on results of these studies Applicant would decide whether to proceed with more detailed studies, and the preparation of an application for license to construct and operate the project. Applicant estimates that the cost of the work to be performed under the preliminary permit would be $60,000.

8 a. Type of Application: Preliminary Permit.

b. Project No: 8761–000.

c. Dated Filed: December 3, 1984.

d. Applicant: Prodek, Inc.

e. Name of Project: Oologah Dam.

f. Location: On the Verdigris Riber in Rogers County, Oklahoma.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Joe D. Tippens, P.O. Box 702680, Tulsa, Oklahoma 74105.

i. Comment Date: March 6, 1985.

j. Description of Project: The proposed project would utilize the existing Oologah Dam and Reservoir owned by the U.S. Army Corps of Engineers and would consist of: (1) A proposed branch penstock approximately 405 feet long and 18 feet in diameter; (2) a proposed powerhouse 140 feet long, and 40 feet wide containing 8 proposed turbine/generators with a total rated capacity of 20,000 kW; (3) a proposed channel tailrace 160 feet long; (4) a new transmission line; and (5) appurtenant facilities. The estimated average annual energy produced by the project would be 60 million kWh operating under a net hydraulic head of about 29 feet. Project power would be sold to a local electric utility company.

k. This notice also consists of the following standard paragraphs: A5, A7, A9, B, C, and D2.

l. *Proposed Scope of Studies under Permit:* A preliminary permit, if issued, does not authorize construction. The term of the proposed preliminary permit is 24 months. The work proposed under the preliminary permit would include economic analysis, preparation of preliminary engineering plans, and a study of environmental impacts. Based on results of these studies Applicant would decide whether to proceed with more detailed studies, and the preparation of an application for license to construct and operate the project. Applicant estimates that the cost of the work to be performed under the preliminary permit would be $90,000.

9 a. Type of Application: Preliminary Permit.

b. Project No: 8679–000.

c. Dated Filed: October 22, 1984.

d. Applicant: Sequia Ranch.

e. Name of Project: Sequia Ranch Water Power Project.

f. Location: On middle Fork of Tule River in Tulare County, California.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Mr. Bruce Borror, Sequia Ranch, Route 2, P.O. Box 300, Springville, California 93265.

i. Comment Date: March 13, 1985.

j. Description of Project: The proposed project would consist of: (1) An existing 20-foot-high, 100-foot-long dam owned by the Southern California Edison Company (SCE) and located at elevation 1,200 feet; (2) a 42-inch-diameter, 7,000-foot-long pipeline; (3) a powerhouse with a total installed capacity of 755 kW under an operating head of 157 feet; and (4) a 100-foot-long, 480-volt tap line connecting with an existing SCE transmission line.

The Applicant estimates a 3 million kWh average annual energy production.

A preliminary permit, if issued, does not authorize construction. Applicant has requested a 36-month permit to conduct feasibility studies and prepare a license application at a cost of $30,000.

k. Purpose of Project: Power would be sold to SCE.

l. This notice also consists of the following standard paragraphs: A5, A7, A9, B, C, and D2.

10 a. Type of Application: Minor License.

b. Project No.: 6675–001.

c. Date Filed: March 29, 1984.

d. Applicant: Jennings-Oftedahl Company.

e. Name of Project: Spruce Water.

f. Location: At the National Forest Service's dam in Gifford Pinchot National Forest, on Trout Creek, in Skamania County, Washington.

g. Filed Pursuant to: Federal Power Act 16 U.S.C. 791(a)–825(r).

h. Contact Person: Michael Jennings, Route 1, Box 221, Centreville, Washington 98613.

i. Comment Date: March 15, 1985.

j. Description of Project: The modifications to the National Service's dam would consist of: (1) A 30-foot ×30-foot ×8-foot concrete based, steel frame intake structure upstream from the center of the dam; (2) a powerhouse built onto the intake structure with a submerged turbine and containing a single generating unit with a capacity of 350 kW and an average annual generation of 1.35 GWh; (3) a draft tube routing the discharge flow through the dam; (4) splashboards along the crest of the dam on the fish ladder side for protection of anadromous fish migration; and (5) a 125-foot-long transmission line.

k. Purpose of Project: Project power would be sold to a utility company for commercial and residential use.

l. This notice also consists of the following standard paragraphs: A3, A9, B, C, and D1.

11 a. Type of Application: Exemption (less than 5 MW).

b. Project No.: 8014–000.

c. Date Filed: Janaury 30, 1984.

d. Applicant: Sterling Enterprises, Inc.

e. Name of Project: Slack Dam.

f. Location: On the Black River in Windsor County, Vermont.

g. Filed Pursuant to: Energy Security Act of 1980, Section 408, 16 U.S.C. 2705 and 2708 *as amended.*

h. Contact Person: Mr. Floryan Lohutko, 24 Mineral Street, Springfield, Vermont 05156.

i. Comment Date: February 25, 1985.

j. Competing Application: Project No. 7998–000, Date Filed: January 26, 1984. Due Date : January 22, 1985.

k. Description of Project: The run-of-river project would consist of: (1) The existing 30-foot-high and 92-foot-long concrete gravity Slack Dam with a crest elevation of 364.1 feet USGS; (2) a small impoundment with a surface area of 0.9 acres: (3) an existing intake and forebay structure with new trash racks and headgates at the west bank about 72 feet upstream from the dam; (4) an exisitng 5-foot-diameter and 120-foot-long steel penstock; (5) an existing powerhouse with 2 new turbine-generator units with a total installed capacity of 400 kW; (6) a new switchyard on top of the powerhouse; (7) a new 70-foot-long and 480–V transmission line; (8) an existing 28-foot-long tailrace; and (9) other appurtenances. Applicant esitmates an average annual generation of 2,128,578 kWh. Existing facilities are owned by the Applicant.

l. Purpose of Project: Project energy would be sold to the Central Vermont Public Corporation.

m. This notice also consists of the following standard paragraphs: A4, B, C, and D3a.

n. Purpose of Exemption: An exemption, if issued, gives the Exemptee priority of control, development, and operation of the project under the terms of the exemption from licensing, and protects the Exemptee from permit or license applicants that would seek to take or develop the project.

12 a. Type of Application: Preliminary Permit.

b. Project No.: 8709–000.

c. Date Filed: November 6, 1984.

d. Applicant: Timothy R. Fallon.

e. Name of Project: Erie Canal, Lock 33.

f. Location: On the Erie Canal, near the Town of Henrietta, Monroe County, New York.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Mr. Timothy R. Fallon, 3 Maplewood Point, Ithaca, New York 14850.

i. Comment Date: March 18, 1985.

j. Description of Project: The proposed project would consist of: (1) An existing 30.5-foot-high, 138-foot-long, integrated concrete gravity structure with an uncontrolled ogee centered spillway section and a fixed spillway section; (2) a reservoir having a surface area of 200 acres, a storage capacity of 2,000 acre-feet, and a normal water surface elevation of 512.6 feet m.s.l.; (3) an existing intake structure; (4) an existing powerhouse containing new generating units having a total capacity of 275 kW; (5) an existing tailrace; (6) a proposed 700-foot-long 4.8–kV transmission line; and (7) appurtenant facilities. The Applicant estimates that the average annual generation would be 1,416,500 kWh. The dam and existing project facilities are owned by the New York State Department of Transportation.

k. Purpose of Project: All project energy generated would be sold to Rochester Gas and Electric Company.

l. This notice also consists of the following standard paragraphs: A5, A7, A9, B, C and D2.

m. Proposed Scope and Cost of Studies under Permit: A preliminary permit, if issued, does not authorize construction. The Applicant seeks issuance of a preliminary permit for a period of 36 months, during which time the Applicant would perform studies to determine the feasibility of the project. Depending upon the outcome of the studies, the Applicant would decide whether to proceed with an application for FERC license. Applicant estimates the cost of the studies under permit would be $10,000.

13 a. Type of Application: Preliminary Permit.

b. Project No.: 8471–000.

c. Date Filed: July 30, 1984.

d. Applicant: New York State Energy Research and Development Authority.

e. Name of Project: Erie Canal Locks E–10 and E–11.

f. Location: Erie Canal in Montgomery County, New York.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Ms. Jacquelyn L. Jerry, Assistant Counsel, New York State Research and Development Authority.

i. Comment Date: March 15, 1985.

j. Competing Application: Project No. 8003–000. Date Filed: January 26, 1984.

k. Description of Project: The proposed project would consist of two developments on the New York State Erie Canal.

The proposed development at Lock E–10 would consist of: (1) An existing 500-foot-wide, 20-foot-high movable dam; (2) an existing lock; (3) an existing 371-acre reservoir at elevation 255 feet m.s.l.; (4) a proposed powerhouse with an installed capacity of 5.5 MW; (5) a proposed tailrace; (6) a proposed 1,600-foot-long, 115–kV transmission line; and (7) appurtenant facilities. The estimated average annual energy is 29,710 MWh.

The proposed development at Lock E–11 would consist of: (1) An existing 590-foot-long, 20-foot-high movable dam; (2) an existing lock; (3) an existing 424-acre reservoir at elevation 267 feet m.s.l.; (4) a proposed powerhouse with an installed capacity of 5.35 MW; (5) a proposed tailrace; (6) a proposed 1,200-foot-long, 115–kV transmission line; and (7) appurtenant facilities. The estimated average annual energy is 23,350 MWh.

l. Purpose of Project: Project energy would be sold to Niagara Mohawk Power Corp.

m. This notice also consists of the following standard paragraphs: A8, A9, B, C, and D2.

n. Proposed Scope of Studies under Permit: A preliminary permit, if issued, does not authorize construction. Applicant seeks issuance of a preliminary permit for a period of 24 months during which time Applicant would investigate project design alternatives, financial feasibility, environmental effects of project construction and operation, and project power potential. Depending upon the outcome of the studies, the Applicant would decide whether to proceed with an application for FERC license. Applicant estimates that the cost of the studies under permit would be $250,000.

14 a. Type of Application: Major Project, 5 MW or Less.

b. Project No: 7500–002.

c. Dated Filed: October 22, 1984.

d. Applicant: Kentucky Hydro Associates.

e. Name of Project: Kentucky River Lock and Dam No. 4.

f. Location: On the Kentucky River, near the Town of Frankfort, Franklin County, Kentucky.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Mr. Bruce J. Wrobel, Kentucky Hydro Associates, 91 Newbury Street, Third Floor, Boston, Massachusetts 02116.

i. Comment Date: March 13, 1985.

j. Description of Project: The proposed project would utilize the U.S. Army Corps of Engineers' Kentucky River Lock and Dam No. 4 and would consist of: (1) A new reinforced concrete powerhouse, 114 feet long and 80 feet wide, containing three turbine/generator units each rated at 1000 kW and operating at an average head of 11 feet; (2) a new steel access tower, about eight feet square and 24 feet high; (3) a new concrete weir, 15 feet long to be located on the left side of the powerhouse; (4) the removal of approximately 95 feet of existing dam adjacent to the riverside lock wall. This will be replaced by a concrete stabilization saddle, approximately 15 feet wide by 30 feet high by 90 feet long, which will act as an anchor for the dam; (5) there new steel trash racks; (6) a new 15–kV

transmission line 425 feet long; (7) a new switching station; and (8) appurtenant electrical and mechanical facilities. The Applicant estimates the average annual energy production to be 14.0 GWh.

k. Purpose of Project: The Applicant intends to sell the power generated at the proposed facility to the Frankfort Electrical and Water Plant Board.

l. This notice also consists of the following standard paragraphs: A3, A9, B, C, and D1.

15 a. Type of Application: Preliminary Permit.

b. Project No: 6293–002.

c. Dated Filed: October 22, 1984.

d. Applicant: Horseshoe Bar Hydro Associates.

e. Name of Project: Horsehoe Bar.

f. Location: On Middle Fork American River, near Foresthill, in Placer County, California.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Mr. David C. Auslam, Jr., 3327 Longview Drive, Suite 250, North Highlands, California (916) 972–0507.

i. Comment Date: March 13, 1985.

j. Competing Application: Project No. 8545–000, Date Filed: August 21, 1984. Due Date: February 8, 1985.

k. Description of Project: The proposed project would utilize the existing Horseshoe Bar Tunnel with a hydraulic capacity of about 25,000 cfs and would consist of: (1) A 35-foot-high, 200-foot-long diversion dam across Middle Fork American River; (2) an intake structure; (3) a powerhouse located at the tunnel inlet containing turbine-generator units with a total installed capacity of 8.0 MW and producing an estimated average annual generation of 40.0 GWh; a similar powerhouse located at the tunnel outlet would also be evaluated; (4) a switchyard; and (5) a 1,500-foot-long, 60–kV transmission line to interconnect the project to an existing Pacific Gas and Electric Company (PG&E) line. The proposed project would be located on American Bar Quartz Mining Company lands and would be surrounded by Tahoe and Eldorado National Forest lands. Project power would be sold to PG&E.

A preliminary permit, issued, does not authorize construction. The Applicant seeks a 24-month permit to study the feasibility of constructing and operating the project and estimates the cost of the studies at $200,000.

l. This notice also consists of the following standard paragraphs: A8, A9, B, C, and D2.

16 a. Type of Application: Minor License.

b. Project No: 6154–005.

c. Date Filed: October 26, 1984.

d. Applicant: Mill and Sulphur Creek Power Plant Partnership.

e. Name of Project: Mill and Sulphur Creek.

f. Location: On Mill and Sulphur Creeks, near Dinsmore, in Humboldt County, California.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Mr. David G. DeMera, P.O. Box 628, Murphys, California 95247, (209) 728–3242.

i. Comment Date: March 13, 1985.

j. Description of Project: The proposed run-of-the-river project would consist of: (1) Two 4-foot-high, 30-foot-long concrete diversion weirs at approximate elevation 3,600 feet msl, one each on Mill Creek and on Sulphur Creek, (2) a 22-inch-diameter low pressure pipeline connecting the two diversion structures; (3) a 22-inch-diameter, 9,600-foot-long steel pipeline/penstock; (4) a powerhouse located adjacent to the Van Duzen River at approximate elevation 2,400 feet msl containing a single Pelton turbine-generator unit with a rated capacity of 1,496 kW and producing an estimated average annual generation of 3.2 GWh; (5) a 4-foot-wide by 45-foot-long open channel tailrace discharging to the Van Duzen River one mile upstream from the river confluence with Mill and Sulphur Creeks; and (6) a 1,100-foot-long, 12.5–kV transmission line to interconnect the project to an existing Pacific Gas and Electric Company (PG&E) line. Project power would be sold to PG&E.The project would be located entirely on Six Rivers National Forest lands. Applicant estimates construction cost at $1,032,264. Applicant does not propose to develop any recreational facilities.

k. This notice also consists of the following standard paragraphs: A3, A9, B, C, and D1.

17 a. Type of Application: Preliminary Permit.

b. Project No: 8733–000.

c. Date Filed: November 26, 1984.

d. Applicant: Mega Renewables.

e. Name of Project: Walker/Digger Power Project.

f. Location: On Digger Creek, near town of Menton, in Shasta and Tehama Counties, California.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Mr. Fred G. Castagna, 2576 Hartnell Avenue, Redding, California 96002.

i. Comment Date: March 13, 1985.

j. Description of Project: The proposed project would consist of: (1) The existing 5-foot-high, 60-foot-long Bull Ditch Water User's Association's intake structure at elevation 3,200 feet; (2) a 51-inch-diameter, 11,000-foot-long diversion conduit; (3) a 45-inch-diameter, 6,000-foot-long steel penstock; (4) a powerhouse with a total installed capacity of 3,000 kW operating under a head of 570 feet; and (5) a 3,000-foot-long, 12–kV transmission line to connect to an existing Pacific Gas and Electric Company (PG&E) transmission line. The Applicant estimates the average annual energy generation at 9.2 million KWh to be sold to PG&E.

A preliminary permit, if issued, does not authorize construction. The Applicant seeks issuance of a 36-month preliminary permit to conduct technical, environmental and economic studies, and also prepare an FERC license application at an estimated cost of $70,000.

k. This notice also consists of the following standard paragraphs: A5, A7, A9, B, C, and D2.

18 a. Type of Application: Amendment of License.

b. Project No: 2004–006.

c. Date Filed: March 6, 1984.

d. Applicant: Holyoke Water Power Company (Licensee).

e. Name of Project: Hadley Falls.

f. Location: At the Holyoke Dam and downstream canal system on the Connecticut River in Hampden County, Massachusetts.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(1)–825(r).

h. Contact Person: W. G. Counsil, Senior Vice President, Northeast Utilities Service Company, P.O. Box 270, Hartford, Connecticut 06141.

i. Comment Date: February 18, 1985.

j. Description of Project: The license for the Hadley Falls Project No. 2004 was issued for a period of 50 years effective July 1, 1949, and has an authorized installed capacity of 58,785 horsepower, as amended. The Licensee proposes to include its existing Chemical Station in the license. The Chemical Station; constructed in 1934, is located between the third level canal and the Connecticut River and consists of: (1) A 22-foot-wide and 260-foot-long flume drawing water from the third level canal; (2) a powerhouse with two 800–kW units; (3) a 125-foot-long tailrace discharging water into the Connecticut River; and (4) other appurtenances. The Chemical Station generates an average of 5,430,000 kWh per year. The facilities are owned by the Licensee and the City of Holyoke.

k. Purpose of Project: The power output of the Chemical Station is fed into the Holyoke Water Power Company distribution lines.

l. This notice also consists of the following standard paragraphs: B, C and D1.

19 a. Type of Application: Transfer of License.

b. Project No: 5944–002.

c. Date Filed: October 15, 1984.

d. Applicant: Pocantico Development Associates, Inc., Richard J. J. Hungerford, and Kris A. Dryland, and Washington Electric Generation and Transmission Cooperative, Inc.

e. Name of Project: Moretown No. 8 Project.

f. Location: On the Mad River in the Town of Moretown, Washington County, Vermont.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Robert O. Toombs, Manager, Washington Electric Generation and Transmission Cooperative, Inc., P.O. Box 9, East Montpelier, Vermont 05651.

i. Comment Date: February 18, 1985.

j. Description of Proposed Transfer: On December 7, 1982, a minor license was issued to Pocantico Development Associates, Inc., Richard J. J. Hungerford, and Kris A. Dryland (Licensees), to construct, operate, and maintain the Moretown #8 Project No. 5944. The Licensees intend to sell the project to Washington Electric Generation and Transmission Cooperative, Inc. (Transferee), a cooperative corporation in the State of Vermont. For that reason, the Licensees and the Transfere have filed a request to transfer the license to Washington Electric Generation and Transmission Cooperative, Inc.

The Licensees have complied with the terms and conditions of the license and have been granted an extension of time to start construction by May 31, 1986. The Transferee has agreed to accept all the terms and conditions of the license and to be bound by it as if it were the original Licensee.

k. This notice also consists of the following standard paragraphs: B and C.

20 a. Type of Application: Preliminary permit.

b. Project No: 8565–000.

c. Date Filed: August 31, 1984.

d. Applicant: Independence Electric Corporation.

e. Name of Project: Lock & Dam No. 8 Hydroelectric Project.

f. Location: On the Kentucky River, in Jessamine and Garrard Counties, Kentucky.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)-825(r)

h. Contact Person: G. William Miller, Independence Electric Corp., 919–18th Street, NW. (Suite 750) Washington, D.C. 20006

i. Comment Date: March 11, 1985.

j. Description of Project: The proposed project would utilize the existing U.S. Army Corps of Engineers Dam No. 8 and Reservoir and would consist of: (1) A proposed forebay channel approximately 80-feet wide by 150-feet long; (2) a new reinforced concrete powerhouse, housing two turbine-generator units with a total installed capacity of 5,600 kW; (3) a proposed tailrace channel approximately 60-feet wide by 150-feet long; (4) a proposed 69-kV transmission line approximately 1.5 miles long; and (5) appurtenant facilities. Applicant estimates that the average annual energy would be 21,500 MWh.

k. Purpose of Project: The applicant anticipates that project energy will be sold to a nearby utility.

l. This notice also consists of the following standard paragraphs: A5, A7, A9, B, C, and D2.

m. Proposed Scope of Studies under Permit: A preliminary permit, if issued, does not authorize construction. Applicant seeks issuance of a preliminary permit for a period of 36 months during which time it would prepare studies of the hydraulic, construction, economic, environmental, historic and recreational aspects of the project. Depending on the outcome of the studies, Applicant would prepare an application for an FERC license. Applicant estimates the cost of the studies under the permit would be $50,000.

21 a. Type of Application: Major Licence (5MW or Less).

b. Project No: 8383–000.

c. Date Filed: June 22, 1984.

d. Applicant: Palisade Irrigation District.

e. Name of Project: Palisade Irrigation District Hydroelectric Power Project.

f. Location: On the Colorado River in Mesa in Mesa County, Colordo.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Michael N. McCarty, McCarty, Noone & Williams Professional Corporation, 490 L'Enfant Plaza East, Suite 3206, Washington, D.C. 20024 & Herman Almaras, 731353/10 Road, Palisade, Colorado 81526.

i. Comment Date: March 11, 1985.

j. Competing Application: Project No. 4515–003, Date Filed: April 28, 1983.

k. Description of Project: The existing dam is owned by the Palisade Irrigation District. The proposed project would consist of: (1) An existing reservoir with a surface area of one acre and negligible storage at powerpool elevation of 4,720 feet M.S.L.; (2) an existing reinforced concrete dam, which is 324 feet long and 8 feet high; (3) 5 proposed modules each containing two intake tubes, two generating units rated at 500–KW each, and two siphon penstocks which divert the water through the modules. The modules would be constructed across the dam. The total installed capacity for the project would be 5 MW; (4) a proposed 300-foot, 25–KV buried cable transmission line; (5) a proposed 2,700-foot-long access road; (6) a proposed tailrace channel; and (7) appurtenant facilities. The estimated average annual energy output for the project is 19,176,216 kWh.

l. Purpose of Project: Power produced at the project would be sold to the Public Service Company of Colorado or to the Colorado-Ute Electric Association.

m. This notice also consists of the following standard paragraphs: A4, B, C, & D3b.

22 a. Type of Application: Preliminary Permit.

b. Project No: 8648–000.

c. Dated Filed: October 5, 1984.

d. Applicant: David Ames.

e. Name of Project: Mill Creek Power Project.

f. Location: On Mill Creek, near Happy Camp, within Klamath National Forest, in Siskiyou County, California.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Mr. David Ames, Star Route Box 220, Kneeland, California 95549.

i. Comment Date: March 11, 1985.

j. Description of Project: The proposed project would consist of: (1) A 5-foot-high, 25-foot-long diversion dam at elevation 2,635 feet; (2) an 8-inch-diameter, 3,500-foot-long penstock; (3) a powerhouse with a total installed capacity of 100 kW operating under a head of 400 feet; and (4) a 1,500-foot-long, 12–kV transmission line from the powerhouse to connect to an existing Pacific Gas and Electric Company (PG&E) transmission line. The Applicant estimates the average annual energy generation at 0.72 million kWh to be sold to PG&E.

A preliminary permit, if issued, does not authorize construction. The Applicant seeks issuance of a 24-month preliminary permit to conduct technical, environmental and economic studies, and also prepare an FERC license application at an estimated cost of $5,000.

k. This notice also consists of the following standard paragraphs: A6, A7, A9, B, C, and D2.

23 a. Type of Application: License (Minor).

b. Project No: 7544–001.

c. Date Filed: August 14, 1984.

d. Applicant: Great Western Power and Light, Inc.

e. Name of Project: Mike Unit.

f. Location: San Pitch River, Sanpete County, Utah.

g. Filed Pursuant to: Federal Power Act, 16 U.S.C. 791(a)–825(r).

h. Contact Person: Mr. Michael J. Graham, 484 East 300 North, Manti, Utah 84642.

i. Comment Date: March 11, 1985.

j. Description of Project: The proposed project would consist of: (1) A proposed small diversion and water collection structure; (2) a proposed 8,800-foot-long ditch section and 40-inch-diameter pipe section and an 18-inch-diameter pipe section; (3) a proposed powerhouse with two generating units with a total capacity of 1,500 kW; (4) a short tailrace section; (5) a 500-foot-long, 12.5–kV transmission line and (6) appurtenant facilities.

k. Purpose of Project: The estimated average annual generation of 11,880,000 kWh would sold to a local utility.

l. This notice also consists of the following standard paragraphs: A3, A9, B, C, and D1.

Competing Applications

A1. Exemption for Small Hydroelectric Power Project under 5MW Capacity—Any qualified license or conduit exemption applicant desiring to file a competing application must submit to the Commission, on or before the specified comment date for the particular application, either a competing license or conduit exemption application that proposes to develop at least 7.5 megawatts in that project, or a notice of intent to file such an application. Any qualified small hydroelectric exemption applicant desiring to file a competing application must submit to the Commission, on or before the specified comment date for the particular application, either a competing small hydroelectric exemption appplication or a notice of intent to file such an application. Submission of a timely notice of intent allows an interested person to file the competing license, conduit exemption, or small hydroelectric exemption application no later than 120 days after the specified comment date for the particular application. Applications for preliminary permit will not be accepted in response to this notice.

A2. Exemption for Small Hydroelectric Power Project under 5MW Capacity—Any qualified license or conduit exemption applicant desiring to file a competing application must submit to the Commission, on or before the specified comment date for the particular application, either a completing license or conduit exemption application that proposes to develop at least 7.5 megawatts in that project, or a notice of intent to file such an application. Submission of a timely notice of intent allows an interested person to file the competing license or conduit exemption application no later than 120 days after the specified comment date for the particular application. Applications for preliminary permit and small hydroelectric exemption will not be accepted in response to this notice.

A3. License or Conduit Exemption—Any qualified license, conduit exemption, or small hydroelectric exemption applicant desiring to file a competing application must submit to the Commission, on or before the specified comment date for the particular application, either a competing license, conduit exemption, or small hydroelectric exemption application, or a notice of intent to file such an application. Submission of a timely notice of intent allows an interested person to file the competing license, conduit exemption, or small hydroelectric exemption application no later then 120 days after the specified comment date for the particular application. Applications for preliminary permit will not be accepted in resonse to this notice.

The provision is subject to the following exception: if an application described in this notice was filed by the preliminary permittee during the term of the permit, a small hydroelectric exemption application may be filed by the permittee only (license and conduit exemption applications are not affected by this restriction).

A4. License or Conduit Exemption—Public notice of the filing of the initial license, small hydroelectric exemption or conduit exemption application, which has already been given, established the due date for filing competing applications or notices of intent. In accordance with the Commission's regulations, any competing application for license, conduit exemption, small hydroelectric exemption, or preliminary permit, or notices of intent to file competing applications, must be filed in response to and in compliance with the public notice of the initial license, small hydroelectric exemption or conduit exemption application. No competing applications or notices of intent may be filed in response to this notice.

A5. Preliminary Permit: Existing Dam or Natural Water Feature Project—Anyone desiring to file a competing aplication for preliminary permit for a proposed project at an existing dam or natural water feature project, must submit the competing application to the Commission on or before 30 days after the specified comment date for the particular application (see 18 CFR 4.30 to 4.33 (1982)). A notice of intent to file a competing application for preliminary permit will not be accepted for filing.

A competing preliminary permit application must conform with 18 CFR 4.33 (a) and (d).

A6. Preliminary Permit: No Existing Dam—Any one desiring to file a competing application for preliminary permit for a proposed project where no dam exists or where there are proposed major modifications, must submit to the Commission on or before the specified comment date for the particular application, the competing application itself, or a notice of intent to file such an application. Submission of a timely notice of intent allows an interested person to file the competing preliminary permit application no later then 60 days after the specified comment date for the particular application.

A competing preliminary permit application must conform with 18 CFR 4.33 (a) and (d).

A7. Preliminary Permit—Except as provided in the following paragraph, any qualified license, conduit exemption, or small hydroelectric exemption appplicant desiring to file a competing application must submit to the Commission, on or before the specified comment date for the particular application, either a competing license, conduit exemption, or small hydroelectric exemption application or a notice of intent ot file such an application. Submission of a timely notice of intent to file a license, conduit exemption, or small hydroelectric exemption application allows an interested person to file the competing application no later than 120 days after the specified comment date for the particular application.

In addition, any qualified license or conduit exemption applicant desiring to file a competing application may file the subject application until: (1) A preliminary permit with which the subject license or conduit exemption application would compete is issued, or (2) the earliest specified comment date for any license, conduit exemption, or small hydroelectric exemption application with which the subject license or conduit exemption application would compete; whichever occurs first.

A competing license application must conform with 18 CFR 4.33 (a) and (d).

A8. Preliminary Permit—Public notice of the filing of the initial preliminary permit application, which has already

been given, established the due date for filing competing preliminary permit applications on notices of intent. Any competing preliminary permit application, or notice of intent to file a competing preliminary permit application, must be filed in response to and in compliance with the public notice of the initial preliminary permit application. No competing preliminary permit applications or notices of intent to file a preliminary permit may be filed in response to this notice.

Any qualified small hydroelectric exemption applicant desiring to file a competing application must submit to the Commission, on or before the specified comment date for the particular application, either a competing small hydroelectric exemption application or a notice of intent to file such an application. Submission of a timely notice of intent to file a small hydroelectric exemption application allows an interested person to file the competing application no later than 120 days after the specified comment date for the particular application.

In addition, any qualified license or conduit exemption applicant desiring to file a competing application may file the subject application until: (1) A preliminary permit with which the subject license or conduit exemption application would compete is issued, or (2) the earliest specified comment date for any license, conduit exemption, or small hydroelectric exemption application with which the subject license or conduit exemption application would compete; whichever occurs first.

A competing license application must conform with 18 CFR 4.33 (a) and (d).

A9. Notice of intent—A notice of intent must specify the exact name, business address, and telephone number of the prospectice applicant, include an unequivocal statement of intent to submit, if such an application may be filed, either (1) a preliminary permit application or (2) a license, small hydroelectric exemption, or conduit exemption application, and be served on the applicant(s) named in this public notice.

B. *Comments, Protests, or Motions to Intervene*—Anyone may submit comments, a protest, or a motion to intervene in accordance with the requirements of the Rules of Practice and Procedure, 18 CFR 385.210, 385.211, 385.214. In determining the appropriate action to take, the Commission will consider all protests or other comments filed, but only those who file a motion to intervene in accordance with the Commission's Rules may become a party to the proceeding. Any comments, protests, or motions to intervene must be received on or before the specified comment date for the particular application.

C. *Filing and Service of Responsive Documents*—Any filings must bear in all capital letters the title "COMMENTS", "NOTICE OF INTENT TO FILE COMPETING APPLICATION", "COMPETING APPLICATION", "PROTEST" or "MOTION TO INTERVENE" as applicable, and the Project Number of the particular application to which the filing is in response. Any of the above named documents must be filed by providing the original and the number of copies required by the Commission's regulations to: Kenneth F. Plumb, Secretary, Federal Energy Regulatory Commission, 825 North Capitol Street, NE., Washington, D.C. 20426. An additional copy must be sent to: Fred E. Springer, Chief, Project Management Branch, Division of Hydropower Licensing, Federal Energy Regulatory Commission, Room 208 RB at the above address. A copy of any notice of intent, competing application or motion to intervene must also be served upon each representative of the Applicant specified in the particular application.

D1. *Agency Comments*—Federal, State, and local agencies that receive this notice through direct mailing from the Commission are requested to provide comments pursuant to the Federal Power Act, the Fish and Wildlife Coordination Act, the Endangered Species Act, the National Historic Preservation Act, the Historical and Archeological Preservation Act, the National Environmental Policy Act, Pub. L. 88–29, and other applicable statutes. No other formal requests for comments will be made.

Comments should be confined to substantive issues relevant to the issuance of a license. A copy of the application may be obtained directly from the Applicant. If an agency does not file comments with the Commission within the time set for filing comments, it will be presumed to have no comments. One copy of an agency's comments must also be sent to the Applicant's representatives.

D2. *Agency Comments*—Federal, State, and local agencies are invited to file comments on the described application. (A copy of the application may be obtained by agencies directly from the Applicant.) If an agency does not file comments within the time specified for filing comments, it will be presumed to have no comments. One copy of an agency's comments must also be sent to the Applicant's representatives.

D3a. *Agency Comments*—The U.S. Fish and Wildlife Service, the National Marine Fisheries Service, and the State Fish and Game agency(ies) are requested, for the purposes set forth in Section 408 of the Energy Security Act of 1980, to file within 60 days from the date of issuance of this notice appropriate terms and conditions to protect any fish and wildlife resources or to otherwise carry out the provisions of the Fish and Widlife Coordination Act. General comments concerning the project and its resources are requested; however, specific terms and conditions to be included as a condition of exemption must be clearly identified in the agency letter. If an agency does not file terms and conditions within this time period, that agency will be presumed to have none. Other Federal, State, and local agencies are requested to provide any comments they may have in accordance with their duties and responsibilities. No other formal requests for comments will be made. Comments should be confined to substantive issues relevant to the granting of an exemption. If an agency does not file comments within 60 days from the date of issuance of this notice, it will be presumed to have no comments. One copy of an agency's comments must also be sent to the Applicant's representatives.

D3b. *Agency Comments*—The U.S. Fish and Wildlife Service, the National Marine Fisheries Service, and the State Fish and Game agency(ies) are requested, for the purposes set forth in section 30 of the Federal Power Act, to file within 45 days from the date of issuance of this notice appropriate terms and conditions to protect any fish and wildlife resources or otherwise carry out the provisions of the Fish and Wildlife Coordination Act. General comments concerning the project and its resources are requested; however, specific terms and conditions to be included as a condition of exemption must be clearly identified in the agency letter. If an agency does not file terms and conditions within this time period, that agency will be presumed to have none. Other Federal, State, and local agencies are requested to provide comments they may have in accordance with their duties and responsibilities. No other formal request for comments will be made. Comments should be confined to substantive issues relevant to the granting of an exemption. If an agency does not file comments within 45 days from the date of issuance of this notice, it will be presumed to have no comments. One copy of an agency's comments must also be sent to the Applicant's representatives.

Dated: January 17, 1985

Kenneth F. Plumb,

Secretary.

[FR Doc. 85-1724 Filed 1-22-85; 8:45 am]

BILLING CODE 6717-01-M

Procurement and Assistance Management Directorate

Restriction of Eligibility for Grant Award

AGENCY: U.S. Department of Energy (DOE).

ACTION: Notice of Restriction of Eligibility for Grant Award.

SUMMARY: DOE announces that it plans to award a grant to the Coastal Zone Foundation in the amount of $10,000 in partial support of the Coastal Zone 85 Conference. Pursuant to § 600.7(b) of the DOE Financial Assistance Rules, 10 CFR Part 600, DOE has determined that eligibility for this grant award shall be limited to the Coastal Zone Foundation.

Procurement Request Number:

01-85FE60677.000

Project Scope

The Coastal Zone Foundation is hosting a four-day symposium on "Coastal and Ocean Management" in Baltimore, Maryland, from July 30-August 2, 1985. This symposium will address the multiple aspects of Coastal and Ocean Management, including research and applications in engineering, the environment, law, society, etc. The Coastal Zone Foundation sponsors such symposia on periodic basis and seeks assistance from governmental bodies, non-profit organizations and corporations. The DOE is vitally interested in proper coastal and ocean management and has determined that this award to Coastal Zone Foundation on a restricted eligibility basis is appropriate.

FOR FURTHER INFORMATION CONTACT: James Beiriger, MA-452.1, U.S. Department of Energy, Office of Procurement Operations, 1000 Independence Avenue, SW., Washington, DC 20585.

Issued in Washington, D.C., on January 16, 1985.

David G. Newman,

Director, Office of Procurement Operations.

[FR Doc. 85-1734 Filed 1-22-85; 8:45 am]

BILLING CODE 6450-01-M

ENVIRONMENTAL PROTECTION AGENCY

[PF-401; FRL-2758-2]

Certain Companies; Pesticide Tolerance Petitions; Dow Chemical Co., et al.

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: EPA has received pesticide and feed additive petitions relating to the establishment and/or amendment of tolerances for certain pesticide chemicals in or on certain raw agricultural commodities.

ADDRESS: By mail, submit comments identified by the document control number [PF-401] and the petition number, attention Product Manager (PM) name in each petition, at the followinig address:

Information Services Section (TS-757C), Program Management and Support Division, Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, D.C. 20460.

In person, bring comments to:

Information Services Section (TS-757C) Rm. 236, CM#2, 1921 Jefferson Davis Highway, Arlington, VA 22202.

Information submitted as a comment concerning this notice may be claimed confidential by marking any part or all of that information as "Confidential Business Information" (CBI). Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR Part 2. A copy of the comment that does not contain CBI must be submitted for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice. All written comments filed in response to this notice will be available for public inspection in the Information Services Section office at the address given above, from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

FOR FURTHER INFORMATION CONTACT:

By mail: Registration Division (TS-767C), Attn: (Product Manager (PM) named in each petition), Environmental Protection Agency, Office of Pesticide Programs, 401, M St., SW., Washington, D.C. 20460.

In person: Contact the PM named in each petition at the following office location/telephone number:

Product manager	Office location/ telephone No.	Address
PM-12, Jay Ellenberger.	Rm. 202, CM#2 (703-557-2386).	EPA, 1921 Jefferson Davis Hwy, Arlington, VA 22202.
PM-16, William Miller.	Rm. 211, CM#2 (703-557-2600).	Do.
PM-21, Henry Jacoby.	Rm. 227, CM#2 (703-557-1900).	Do.
PM-25, Robert Taylor.	Rm. 245, CM#2 (703-557-1800).	Do.

SUPPLEMENTARY INFORMATION: EPA has received pesticide (PP) and feed additive petitions (FAP) relating to the establishment and/or amendment of tolerances for certain pesticide chemicals in or on certain agricultural commodities.

I. Initial filings

1. *PP 5F3164 & FAP 5H5448.* Dow Chemical Co., P.O. Box 1706, Midland, MI 48640. Proposes amending 40 CFR Part 180 (raw agricultural commodity) and 21 CFR Part 561 (animal food commodity) by establishing tolerances for the combined residues of the miticide cyhexatin (tricyclohexylhydroxystannane) and its organotin metabolites (calculated as cyhexatin) in or on the commodities as follows:

Petition ID	CFR affected	Commodities	Parts per million (ppm)
PP 5F3164	40 CFR 180.144.	Grapes	1.5
FAP 5H5448	21 CFR 561.400.	Grape pomace.	5
		Raisin waste	6

The proposed analytical method for determining residues is gas chromatography. (PM-12).

2. *PP 3F2942.* Mobay Chemical Corp. P.O. Box 4913, Hawthorn Rd., Kansas City, MO 64120. Proposes amending 40 CFR 180.338 by establishing tolerances for the residues of the fungicide/insecticide 6-methyl-1,3-dithiolo [4,5-beta] quinoxalin-2-one in or on the commodities cherries at 0.02 ppm and grapes at 0.1 ppm. The proposed analytical method for determining residues is gas chromatography. (PM-12).

3. *PP 5F3190.* Mobay Chemical Corp. Proposes amending 40 CFR 180.320 by establishing tolerances for the combined residues of the insecticide 3,5-dimethyl-4-(methylthio) phenyl methylcarbamate and its cholinesterase-inhibiting metabolites in or on the commodities grass at 35 ppm, pecans at 2 ppm, and ground pecan shells at 8 ppm. The proposed analytical method for determing residues is gas

chromatographic procedure using a flame photometric detector operated in the sulfur mode. (PM–16).

4. *PP 5F3183.* SDS Biotech Corp., 7528 Auburn RD., P.O. Box 348, Dainesville, OH 44077. Proposes amending 40 CFR 180.275 by establishing a tolernace for the combined residues of the fungicide chlorothalonil (2,4,5,6-tetrachloroisophtholonitrile and its metabolite (4-hydroxy-2,5,6-trichloroisophthalonitrile) in or on the commodity cherries (sour and sweet) at 3.0 ppm. The proposed analytical method for determining residues is gas chromatography using electron capture with (^{63}Ni) detection. (PM–21).

II. Amended Petitions

1. *PP 6F1851.* Shell Chemical Co., 1025 Connecticut Ave., NW., Washington, DC 20036. EPA issued a notice published in the **Federal Register** of November 26, 1976 (41 FR 52102), which announced that Shell Chemical Co., had submitted PP 6F1851 to the Agency proposing to amend 40 CFR 180.296 by establishing tolerances for residues of the insecticide dimethyl phosphate of 3-hydroxy-*N*-methyl/cis/crotonamide in or on the commodities sweet corn kernels at 0.3 ppm, field corn grain at 0.2 ppm and field corn fodder and field corn forage (including silage) at 2.0 ppm.

Shell Chemical Co. has amended the petition by increasing the proposed tolerance in or on corn grain from 0.2 ppm to 0.3 ppm; and by revising the crop identifications as follows:

Commodities	Parts per million (ppm)
Corn, fodder	2.0
Corn, forage	2.0
Corn, fresh (including sweet K + CWHR)	0.3
Corn, grain	0.3

The proposed analytical method for determining residues is a gas liquid chromatographic procedure using a phosphorus sensitive flame photometric procedure. (PM–16)

2. *PP 2F2711* Union Carbide Co., P.O. Box 12014, TW Alexander Drive, Research Triangle Park, NC 27709. EPA issued a notice published in the **Federal Register** of July 28, 1982 (47 FR 32603), which announced that Union Carbide Co., had submitted PP 2F2711 to the Agency proposing to amend 40 CFR 180.300 by establishing tolerances for residues of the plant growth regulator ethephon ((2-chloroethyl) phosphomic acid) in or on the commodities grain of wheat and barley at 1.0 ppm; straw of barley and wheat at 10.0 ppm

Union Carbide Co. has amended the petition by increasing the tolerance level on grain of barley and wheat from 1.0 to 2.0 ppm and proposing tolerances for milk at 0.1 ppm and liver and kidney of cattle, goats, hogs, and horses at 2.0 ppm. The proposed analytical method for determining residues is gas chromatography using a flame detector (phosphorus mode). (PM–25).

(Secs. 408(d)(2) 68 Stat. 512 (21 U.S.C. 346a(d)(2)); 409(c)(1), 72 Stat. 1786 (21 U.S.C. 348(c)(1)))

Dated: January 10, 1985.

Douglas D. Campt,

Director, Registration Division, Office of Pesticide Programs.

[FR Doc. 85–1434 Filed 1–22–85; 8:45 am]

BILLING CODE 6560-50-M

[OPP–30247; FRL–2760–1]

Certain Companies; Applications to Register Pesticide Products; Ciba-Geigy Corp., et al.

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This notice announces receipt of applications to register certain pesticide products containing active ingredients not included in any previously registered products and products involving a changed use pattern pursuant to the provisions of section 3(c)(4) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended.

DATE: Comment by February 22, 1985.

ADDRESS: By mail submit comments identified by the document control number [OPP–30247] and the file number, attention Product Manager (PM) named in each application at the following address:

Information Services Section (TS–757C), Program Management and Support Division, Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, D.C. 20460.

In person, bring comments to: Environmental Protection Agency, Rm. 236, CM #2, 1921 Jefferson Davis Highway, Arlington, VA 22202.

Information submitted in any comment concerning this notice may be claimed confidential by marking any part or all of that information as "Confidential Business Information" (CBI). Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR Part 2. A copy of the comment that does not contain CBI must be submitted for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice to the submitter. All written comments will be available for public inspection in Rm. 236 at the address given above, from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

FOR FURTHER INFORMATION CONTACT:

By mail: Registration Division (TS–767C), Attn: (Product Manager (PM) named in each registration), Office of Pesticide Programs, 401 M St., SW., Washington, D.C. 20460.

In person: Contact the PM named in each registration at the following office location/telephone:

Product manager	Office location/ telephone number	Address
PM 17, Timothy Gardner.	Rm. 207, CM# 2 (703–557–2690).	EPA, 1921 Jefferson Davis Hwy., Arlington, VA 22202
PM 21, Henry Jacoby.	Rm. 229, CM# 2 (703–55–1900).	Do.

SUPPLEMENTARY INFORMATION: EPA received applications as follows to register pesticide products containing active ingredients not included in any previously registered products and products involving a changed use pattern pursuant to the provisions of section 3(c)(4) of FIFRA. Notice of receipt of these applications does not imply a decision by the Agency on the applications.

I. Products Containing Active Ingredients Not Included in Any Previously Registered Products

1. File Symbol: 100–ALA. Applicant: Ciba-Geigy Corp., PO Box 18300, Greensboro, NC 27419. Product name: Armor™ Insect Growth Regulator. Insecticide. Active ingredient: *N*-cyclopropyl-1,3,5-triazine-2,4,6-triamine 5%. Proposed classification/Use: General. For experimental use only to control sciarid fly in mushrooms. Type registration: Conditional. (PM 17)

2. File Symbol: 100–ALU. Applicant: Ciba-Geigy Corp. Product name: Trigard™ 75W Insecticide. Insecticide. Active ingredient: *N*-cyclopropyl-1,3,5-triazine-2,4,6-triamine 75%. Proposed classification/Use: General. For leafminer control in chrysanthemums. Type registration: Conditional. (PM 17)

3. File Symbol: 1624–REN. Applicant: United States Borax and Chemical Corp., 3075 Wilshire Blvd., Los Angeles, CA 90010. Product name: 20 Mule Team® Firebrake® ZB. Fungicide. Active ingredient: Zinc borate ($2ZnO \times 3B_2O_3 \times 3.5H_2O$) 100.00%. Proposed classification/Use: General. For manufacturing or formulating use,

and as a fire retardant and microbiocide. (PM 21)

II. Product Involving a Changed Use Pattern

File Symbol: 48313–I. Applicant: Janssen Pharmaceutica, Box 344, Washington Crossing, NJ 08560. Product name: Fungaflor Smoke™. Fungicide. Active ingredient: Imazalil 1-(2-(2,4-dichlorophenyl)-2-(2-propenyloxy)ethyl)-1*H*-imidazole) 15.0%. Proposed classification/Use: General. To include in its presently registered use, new use for control of powdery mildew, and suppression of *Botrytis*, by smoke bombs in greenhouses. Type registration: Conditional. (PM 21)

Notice of approval or denial or an application to register a pesticide product will be announced in the **Federal Register**. The procedure for requesting data will be given in the **Federal Register** if an application is approved.

Comments received within the specified time period will be considered before a final decision is made; comments received after the time specified will be considered only to the extent possible without delaying processing of the application.

Written comments filed pursuant to this notice, will be available in the Program Management and Support Division (PMSD) office at the address provided from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays. It is suggested that persons interested in reviewing the application file, telephone the PMSD office (703–557–3262), to ensure that the file is available on the date of intended visit.

(Sec. 3(c)(4) of FIFRA, as amended)

Dated: January 11, 1985.

Douglas D. Campt,

Director, Registration Division, Office of Pesticide Programs.

[FR Doc. 85–1576 Filed 1–22–85; 8:45 am]

BILLING CODE 6560–50–M

[OPTS–51549; FRL–2735–8]

Certain Chemicals; Premanufacture Notices

Correction

In FR Doc. 84–32471 beginning on page 48801 in the issue of Friday, December 14, 1984, make the following correction: On page 48803, first column, under **PMN 85–248**, thirteenth line, "L5178Y TK±/" should read "L5178Y TK+/−".

BILLING CODE 1505–01–M

[OPTS–51551; FRL–2745–6]

Certain Chemicals; Premanufacture Notices; Receipts

Correction

In FR Doc. 84–33754 beginning on page 50444 in the issue of Friday, December 28, 1984, make the following correction: On page 50446, second column, under **PMN 85–330**, seventh line, "<5,000" should read ">5,000".

BILLING CODE 1505–01–M

[OA–FRL–2762–1]

Updated List of Programs and Activities

Updated List of EPA Programs and Activities Eligible for Intergovernmental Review Under 40 CFR Part 29 and Subject to Section 204 of the Demonstration Cities and Metropolitan Development Act.

The Environmental Protection Agency (EPA) is updating the list of programs and activities which states may select for intergovernmental review under a process established in accordance with Executive Order 12372. Programs subject to the requirements of section 204 of the Demonstration Cities and Metropolitan Development Act are designated with an asterisk (*).

Two new financial assistance programs have been added to the original list published on June 24, 1983 (48 FR 29304): 66.455—Marine Combined Sewer Overflow Special Fund and 66.702—Asbestos Hazards Abatement (Schools) Assistance Program. States choosing to include either of these programs for review under their intergovernmental review process should send written notification within 30 days to the following EPA office: Grants Policy and Procedures Branch, Grants Administration Division (PM–216), U.S. Environmental Protection Agency, 401 M Street, SW., Washington, DC 20460.

Financial Assistance Programs

1. *State and Local Assistance Programs.*

CFDA No.	Title
*66.001	Air Pollution Control Program Grants.
*66.418	Construction Grants for Wastewater Treatment Works.
*66.419	Water Pollution Control—State and Interstate Program Grants.
*66.454	Water Quality Management Planning.
*66.432	State Public Water System Supervision Program Grants.
*66.433	State Underground Water Source Protection—Program Grants.
*66.438	Construction Management Assistance Grants.
(*)	State Inventories of Uncontrolled Hazardous Waste Sites.
*66.455	Marine Combined Sewer Overflow Special Fund.
*66.600	Environmental Protection Consolided Grants—Program Support.
*66.603	Loan Guarantees for Construction of Treatment Work.
*66.700	Pesticides Enforcement Program Grants.
*66.702	Asbestos Hazards Abatement (Schools) Assistance Program.
*66.801	Hazardous Waste Management Financial Assistance to State.
*66.802	Hazardous Substance Response Trust Fund (Super fund).

2. *Research, Development, and Demonstration Projects.* (Selection is limited to proposals which (a) Require an Environmental Impact Statement (EIS); or (b) do not require an EIS but will be newly initiated at a particular site and require unusual measures to limit the possibility of adverse exposure or hazard to the general public; or (c) have a unique geographic focus and ar : directly relevant to the governmental responsibilities of a State or local government within that geographic area.)

CFDA No.	Title
66.500	Environmental Protection—Consolidated Research Grants.
66.501	Air Pollution Control Research Grants.
66.502	Pesticides Control Research Grants.
66.504	Solid Waste Disposal Research Grants.
*66.505	Water Pollution Control—Research, Development, and Demonstration Grants.
*66.506	Safe Drinking Water Research and Demonstration Grants.
66.507	Toxic Substance Research Grants.

Direct Development Activities

*1. Real Property Acquisition or Disposition, Including Obtaining Major Leases or Easements.

*2. Construction of New EPA Facilities.

*3. EPA Issued Plans and Permits Which Do Not Impact Interstate Areas.

Dated: January 15, 1985.

Howard M. Messner,

Assistant Administrator, Administration and Resources Management.

[FR Doc. 85–1693 Filed 1–22–85; 8:45 am]

BILLING CODE 6560–50–M

[OPP–50628; FRL–2761–6]

Issuance of Experimental Use Permits; BASF Wyandotte Corp., et al.

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: EPA has granted experimental use permits to the following applicants. These permits are in accordance with, and subject to, the provisions of 40 CFR Part 172, which

defines EPA procedures with respect to the use of pesticides for experimental purposes.

FOR FURTHER INFORMATION CONTACT: By mail, the product manager cited in each experimental use permit at the address below: Registration Division (TS–767C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, D.C. 20460.

In person or by telephone: Contact the product manager at the following address at the office location or telephone number cited in each experimental use permit: 1921 Jefferson Davis Highway, Arlington, VA.

SUPPLEMENTARY INFORMATION: EPA has issued the following experimental use permits:

70969–EUP–18. Extension. BASF Wyandotte Corporation, 100 Cherry Hill Road, P.O. Box 181, Parsippany, NJ 07054. This experimental use permit allows the use of 3,500 gallons of the fungicide N-cyclohexyl-N-methoxy-2,5-methyl-3-furancarboxamide on cottonseed to evaluate the control of *Rhizoctonia solani*. A total of 7,500 tons of seed are involved; the program is authorized only in the States of Arizona, California, Mississippi, and Texas. The experimental use permit is effective from December 6, 1984 to July 1, 1985. (Henry Jacoby, PM 21, Rm. 229, CM#2 (703–557–1900).)

464–EUP–84. Issuance. Dow Chemical Company, P.O. Box 1706, Midland, MI 48640. This experimental use permit allows the use of 67.5 pounds of the herbicide methyl 2-[4-[(3-chloro-5-trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propanoate on highway and railroad rights-of-way and industrial sites to evaluate the control of weeds. A total of 270 acres are involved; the program is authorized only in the States of Alabama, California, Connecticut, Florida, Georgia, Illinois, Indiana, Iowa, Kentucky, Louisiana, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Nebraska, New York, North Carolina, North Dakota, Ohio, Oregon, South Carolina, South Dakota, Texas, Virginia, Washington, and Wisconsin. The experimental use permit is effective from March 1, 1985 to February 28, 1986. (Richard Mountfort, PM 23, Rm. 253, CM#2 (703–557–1830).)

1471–EUP–50. Amendment. Elanco Products Company, 740 South Alabama St., Indianapolis, IN 46285. In the **Federal Register** of May 2, 1984 (48 FR 18781), EPA issued an experimental use permit pertaining to the extension of 1471–EUP–50 to Elanco Products Company. At the request of the company, the permit has been amended to add the State of Massachusetts and the addition of a claim for the control of *Poa annua* on overseeded Bermudagrass turf. This experimental use permit allows the use of 7,484 pounds of the fungicide fenarimol on various turf grasses to evaluate the control of various turf diseases and the control of *Poa annua* on overseeded Bermudagrass turf. A total of 2,994 are involved; the program is now authorized in the District of Columbia, and all 50 States, except Alaska, Hawaii, and Vermont. The experimental use permit is effective from February 27, 1984 to March 31, 1985. (Henry Jacoby, PM 21, Rm. 229, CM#2 (703–557–1900).)

1471–EUP–63. Extension. Elanco Products Company, 740 South Alabama St., Indianapolis, IN 46285. This experimental use permit allows the use of 3,615 pounds of the herbicide ethalfluralin on peanuts to evaluate the control of weeds. A total of 4,820 acres are involved; the program is authorized only in the States of Alabama, Florida, Georgia, North Carolina, Oklahoma, South Carolina, Texas, and Virginia. The experimental use permit is effective from March 1, 1985 to March 1, 1986. A temporary tolerance for residues of the active ingredient in or on peanuts has been established. (Richard Mountfort, PM 23, Rm. 237, CM#2 (703–557–1830).)

10182–EUP–37. Issuance. ICI Americas Inc., Concord Pike and New Murphy Road, Wilmington, DE 19897. This experimental use permit allows the use of 1,390 pounds of the herbicide (±) butyl-2-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy] propanoate on various crops to evaluate postemergence control of annual and perennial grasses. A total of 2,780 acres are involved; the program is authorized in all 50 States, except the State of Alaska. The experimental use permit is effective from November 6, 1984 to November 30, 1985. This permit is issued with the limitation that all treated crops are destroyed or used for research purposes only. (Richard Mountfort, PM 23, Rm. 253, CM#2 (703–557–1830).)

20954–EUP–20. Amendment. Zoecon Corporation, 975 California Ave., Palo Alto, CA 94304. In the **Federal Register** of November 14, 1984 (48 FR 45063), EPA issued an experimental use permit pertaining to the extension of 20954–EUP–20 to Zoecon Corporation. At the request of the company, the permit has been amended to all 17 States to the program. The experimental use permit allows the use of 175 pounds of the plant growth regulator methoprene on various stored commodities to evaluate the control of various insects. A total of 4,666 tons are involved; the program is now authorized only in the States of Alabama, Arkansas, California, Florida, Georgia, Indiana, Iowa, Kansas, Kentucky, Louisiana, Minnesota, Mississippi, Missouri, Nebraska, North Dakota, Ohio, Oregon, South Dakota, Tennessee, Texas, Washington, and Wisconsin. The experimental use permit is effective from September 21, 1984 to September 21, 1986. (Timothy Gardner, PM 17, Rm. 207, CM#2, (703–557–2690).)

Persons wishing to review these experimental use permits are referred to the designated product managers. Inquiries concerning these permits should be directed to the persons cited above. It is suggested that interested persons call before visiting the EPA office, so that the appropriate file may be made available for inspection purposes from 8:00 a.m. to 4:00 p.m., Monday through Friday, excluding legal holidays.

(Sec. 5, Pub. L. 95–396; 92 Stat. 828 (7 U.S.C. 136c))

Dated: January 11, 1985.

Douglas D. Campt,

Director, Registration Division, Office of Pesticide Programs.

[FR Doc. 85–1684 Filed 1–22–85; 8:45 am]

BILLING CODE 6560–50–M

[OPP–240052 FRL–2739–2]

State Registration of Pesticides

Correction

In FR Doc. 84–32990 beginning on page 49369 in the issue of Wednesday, December 19, 1984, make the following corrections:

1. On page 49370, second column, in the seventh complete paragraph, the date should read "April 27, 1984".

2. On page 49371, first column under the heading **Michigan**, in the first paragraph, the date should read "April 9, 1984".

BILLING CODE 1505–01–M

[OPP–240057; FRL–2761–3]

State Registration of Pesticides; Arkansas, et al.

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: EPA has received notices of registration of pesticides to meet special local needs under section 24(c) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, from 14 States. A registration issued under this section of FIFRA shall not be effective for more than 90 days if the Administrator disapproves the registration or finds it to be invalid

within that period. If the Administrator disapproves a registration or finds it to be invalid after 90 days, a notice giving that information will be published in the Federal Register.

DATE: The last entry for each item is the date the State registration of that product became effective.

FOR FURTHER INFORMATION CONTACT: Sandra English, Registration Division (TS–767C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, D.C.

Office location and telephone number: Rm. 726A, CM #2, 1921 Jefferson Davis Highway, Arlington, VA. (703–557–7116).

SUPPLEMENTARY INFORMATION: Most of the registrations listed below were received by the EPA in September 1984. Receipts of State registrations will be published periodically. The following registrations will be published periodically. The following registrations do not involve a changed-use pattern. The term "changed-use pattern" is defined in 40 CFR 162.3(k) as a significant change from a use pattern approved in connection with the registration of a pesticide product. Examples of significant changes include, but are not limited to, changes from nonfood to food use, outdoor to indoor use, ground to aerial application, terrestrial to aquatic use, and nondomestic to domestic use.

Arkansas

EPA SLN No. AR 84 0018. Monsanto Co. Registration is for Roundup Herbicide to be used on grain sorghum to control weeds. September 11, 1984.

California

EPA SLN No. CA 84 0206. Riverside County Agricultural Commission. Registration is for Rodent Bait Fumarin Treated Grain (0.025%) to be used in bait boxes in concealed places such as corners, attics, near runways or borrows to control house mice, Norway rats, roof rats, ground squirrels, chipmunks, muskrats, meadow mice, wood rats, and jackrabbits. September 11, 1984.

EPA SLN No. CA 84 0209. Riverside County Agricultural Commission. Registration is for Rodent Bait Block Fumarin Treated Grain/Paraffin (0.025%) to be used around barns, poultry houses, sheds, lumber and rubbish piles, and infested ditch banks to control Norway rats, wood rats, and muskrats. September 11, 1984.

EPA SLN No. CA 84 0210. Riverside County Agriculture Comm. Registration is for Pocket Gopher Bait Strychnine Treated Grain (0.50%) to be used in runways below ground to control pocket gophers. September 11, 1984.

EPA SLN No. CA 84 0212. Riverside County Agriculture Comm. Registration is for Rodent Bait Warfarin P Treated Grain (0.025%) to be used in concealed places such as corners and along walls and burrows to control Norway rats, roof rats, and house mice. September 11, 1984.

EPA SLN No. CA 84 0213. Riverside County Agriculture Comm. Registration is for Rodent Bait Warfarin Treated Grain (0.025%) to be used in concealed places such as corners, along walls, in attics, near runways, and at burrows to control Norway rats, roof rats, and house mice, ground squirrels, chipmunks, muskrats, meadow mice, wood rats, and jack rabbits. September 11, 1984.

Connecticut

EPA SLN No. CT 84 0003. Pfizer, Inc. Registration is for Terramycin Tree Injection Formula to be used on peach trees to control peach X-disease. September 6, 1984.

Florida

EPA SLN No. FL 84 0019. Mobay Chemical Co. Registration is for Nemacur 3 Emulsifiable to be used on transplanted cabbage to control nematodes. September 27, 1984.

EPA SLN No. FL 84 0020. E.I. du Pont de Nemours & Co. Registration is for du Pont Manzate 200 Fungicide to be used on flowers, foliage plants, and ornamental crops to control assorted plant diseases. July 30, 1984.

EPA SLN No. FL 84 0023. United States Sugar Corp. Registration is for Difolatan 80 Sprills to be used on sugar cane as a plant growth regulator. September 7, 1984.

Georgia

EPA SLN No. GA 84 0004. Mobay Chemical Co. Registration is for Guthion 2L Insecticide to be used on cotton to control boll weevils. September 13, 1984.

EPA SLN No. GA 84 0005. Dow Chemical Co. Registration is for Dursban TC Termiticide Concentrate to be used on structures to control termites. September 19, 1984.

Indiana

EPA SLN No. IN 84 0007. Mobay Chemical Co. Registration is for Mesurol 75% Wettable Powder to be used on corn to control snails and slugs. September 11, 1984.

Kansas

EPA SLN No. KS 84 0002. ICI Americas, Inc. Registration is for Gramoxone Paraquat Herbicide to be used on alfalfa to control weeds between cuttings. September 13, 1984.

EPA SLN No. KS 84 0003. Velsicol Chemical Corp. Registration is for Banvel Herbicide to be used on wheat to control annual broadleaf weeds. September 13, 1984.

Louisiana

EPA SLN No. LA 84 0019. Monsanto Co. Registration is for Roundup Herbicide to be used on grain surghum (milo) to control annual and perennial grasses. September 13, 1984.

Nebraska

EPA SLN No. NE 84 0008. Pfizer, Inc. Registration is for Floguard 1015 to be used on oil fields to control bacteria. September 28, 1984.

New Hampshire

EPA SLN No. NH 84 0003. Mobay Chemical Corp. Registration is for Mesurol 75% Wettable Powder to be used on tree seeds (nonedible) for nursery plantings to control cowbirds, crows, grackles, mourning doves, and sparrows. September 17, 1984.

New Jersey

EPA SLN No. NJ 84 0017. Clorox Liquid Co. Registration is for Clorox Liquid Bleach to be used on asparagus seeds to control asparagus root rot (*Fusarium oxysporin* and *Fusarium asparagi*). September 5, 1984.

EPA SLN No. NJ 84 0018. E.I. du Ponte de Nemours & Co. Registration is for Dupont Vydate L Insecticide, Nematicide to be used on tomatoes to control potato beetles and aphids. September 10, 1984.

EPA SLN No. NJ 84 0019. E.I. Du Pont de Nemours & Co. Registration is for Du Pont Benlate Fungicide to be used on asparagus seeds to control Fusarium wilt, crown and root rots. September 14, 1984.

Oregon

EPA SLN No. OR 84 0042. PPG Industries, Inc. Registration is for Furloe Chloro-IPC 4EC to be used on sugarbeets grown for seed to control chickweed. September 19, 1984.

EPA SLN No. OR 84 0043. Union Carbide Agricultural Products Co., Inc. Registration is for Emulsamine E–3 Broadleaf Herbicide to be used as a preplant treatment on wheat and barley fields to control broadleaf weeds. September 24, 1984.

EPA SLN No. OR 84 0044. Union Carbide Agricultrual Products Co., Inc. Registration is for Weedar 64 Herbicide to be used as a preplant treatment on wheat and barley fields to control broadleaf weeds. September 24, 1984.

EPA SLN No. OR 84 0045. Union Carbide Agricultural Products Co., Inc. Registration is for Weedar 64 Herbicide to be used as a preplant treatment on wheat and barley fields to control broadleaf weeds. September 24, 1984.

Texas

EPA SLN No. TX 84 0019. Nor-Am Chemical Co. Registration is for Ficam ULV Solution to be used in Texas to control adult mosquitoes. September 14, 1984.

Washington

EPA SLN No. WA 84 0062. Drexel Chemical Co. Registration is for Drexel Dynamite 5 to be used on alfalfa, trefoil, and clover seed crops as a desiccant. September 6, 1984.

EPA SLN No. WA 84 0063. Lipha Chemicals, Inc. Registration is for Rozol Tracking Powder to be used inside homes and structures in attics, boxed eaves, and similar places to control bats. September 12, 1984.

EPA SLN No. WA 84 0064. ArChem Corp. Registration is for Parapel Paraffinized Pellets to be used in pome and stone fruit orchards to control orchard mice. September 18, 1984.

EPA SLN No. WA 84 0065. Degesch America, Inc. Registration is for Degesch Magtoxin Pellets-Prepac to be used in bins and silos to control beetles. September 19, 1984.

EPA SLN No. WA 84 0067. Dow Chemical Co. Registration is for Tordon 22K Weed Killer to be used on nonirrigated grain land to control susceptible broadleaf weeds. September 24, 1984.

(Sec. 24, as amended, 92 Stat. 835 (7 U.S.C. 136))

Dated: January 11, 1985.

Susan H. Sherman,

Acting Director, Office of Pesticide Programs.

[FR Doc. 85-1687 Filed 1-22-85; 8:45 am]

BILLING CODE 6560-50-M

FEDERAL HOME LOAN BANK BOARD

[No. AC-418]

Talladega Federal Savings and Loan Association Talladega, AL; Final Action Approval of Conversion Application

Dated: January 15, 1985.

Notice is hereby given that on December 20, 1984, the Office of General Counsel of the Federal Home Loan Bank Board, acting pursuant to the authority delegated to the General Counsel or his designee, approved the application of Talladega Federal Savings and Loan Association, Talladega, Alabama, for permission to convert to the stock form of organization. Copies of the application are available for inspection at the Secretariat of the Board, 1700 G Street, NW., Washington, D.C. 20552, and at the Office of the Supervisory Agent of the Federal Home Loan Bank of Atlanta, Post Office Box 56527, Peachtree Center Station, 260 Peachtree Street, NE., Atlanta, Georgia, 30343-0527.

By the Federal Home Loan Bank Board.

John F. Ghizzoni,

Assistant Secretary.

[FR Doc. 85-1643 Filed 1-22-85; 8:45 am]

BILLING CODE 6720-01-M

FEDERAL MARITIME COMMISSION

Agreement(s) Filed

The Federal Maritime Commission hereby gives notice of the filing of the following agreement(s) pursuant to section 5 of the Shipping Act of 1984.

Interested parties may inspect and obtain a copy of each agreement at the Washington, D.C. Office of the Federal Maritime Commission, 1100 L Street, NW., Room 10325. Interested parties may submit comments on each agreement to the Secretary, Federal Maritime Commission, Washington, D.C. 20573, within 10 days after the date of the **Federal Register** in which this notice appears. The requirements for comments are found in § 572.603 of Title 46 of the Code of Federal Regulations. Interested persons should consult this section before communicating with the Commission regarding a pending agreement.

Agreement No.: 207-010137-009.

Title: Barber Blue Sea (BBS).

Parties:

Barber Lines A/S

Blue Funnel Line

Rederiaktiebolaget Transatlantic

Synopsis: The proposed amendment would eliminate the agreement's 1988 expiration date and the requirement that BBS utilize only multipurpose vessels and would replace Swedish East Asia Co., Ltd. with its parent company, Rederiaktiebolaget Transatlantic, as a party to the agreement. It would modify the voluntary withdrawal provision, add a provision covering the rights of parties to engage in carrier services and modify the agreement to conform with the format requirements of the Commission's regulations.

Agreement No.: 224-010607-002.

Title: Anacortes Terminal Agreement.

Parties:

Port of Anacortes (Port)

Bellingham Stevedoring Company (BSC)

Synopsis: This amendment provides that 40 percent of Service and Facilities Charges will be accrued to the Port, with the balance of 60 percent going to BSC, for use of the facilities located at Anacortes, Washington.

Agreement No.: 224-010716.

Title: The San Francisco Marine Terminal Agreement.

Parties:

The San Francisco Port Commission (Port)

Evergreen Marine Corp. (Evergreen)

Synopsis: This agreement provides for the utilization by Evergreen of the Port of San Francisco as its published regularly scheduled Northern California port of call. Evergreen guarantees to the Port a minimum annual throughput of 22,500 TEU's for which the whafage charge for Port usage will be on a sliding scale, per TEU basis and dockage charges will be at reduced rates based on the number of vessel calls per year. The agreement has a term of five years.

Dated: January 17, 1985.

By Order of the Federal Maritime Commission.

Bruce A. Dombrowski,

Assistant Secretary.

[FR Doc. 85-1254 Filed 1-22-85; 8:45 am]

BILLING CODE 6730-01-M

Agreement(s) Filed

The Federal Maritime Commission hereby gives notice of the filing of the following agreement(s) pursuant to section 5 of the Shipping Act of 1984.

Interested parties may inspect and obtain a copy of each agreement at the Washington, D.C. Office of the Federal Maritime Commission, 1100 L Street, NW., Room 10325. Interested parties may submit comment on each agreement to the Secretary, Federal Maritime Commission, Washington, D.C. 20573, within 15 days after the date of the **Federal Register** in which this notice appears. The requirements for comments are found in § 572.603 of Title 46 of the Code of Federal Regulations. Interested persons should consult this section before communicating with the Commission regarding a pending agreement.

Agreement No.: 202-010717.

Title: United States South Atlantic and Gulf/Central America Conference.

Parties:

Concorde Line Central America Services

Coordinated Caribbean Transport, Inc.

Seaboard Marine Line, Ltd.

Sea-Land Service, Inc.

Synopsis: The proposed agreement would establish a conference agreement between the parties in the trade between U.S. Atlantic, Gulf, Puerto Rico and Virgin Island ports; and ports in Panama, Costa Rica, Nicaragua, Honduras, El Salvador and Guatemala; and inland or coastal points via such ports. The conference would be divided into six trade areas (one for each foreign country served) each with three rate-making sections (U.S. South Atlantic, U.S. Gulf, and Puerto Rico and U.S. Virgin Islands.)

Dated: January 17, 1985.

By Order of the Federal Maritime Commission.

Bruce A. Dombrowski,

Assistant Secretary.

[FR Doc. 85-1565 Filed 1-22-85; 8:4 am]

BILLING CODE 6730-01-M

FEDERAL RESERVE SYSTEM

Intermountain Bancshares, Inc., et al.; Formations of; Acquisitions by; and Mergers of Bank Holding Companies

The companies listed in this notice have applied for the Board's approval under section 3 of the Bank Holding Company Act (12 U.S.C. 1842) and § 225.14 of the Board's Regulatory Y (12 CFR 225.14) to become a bank holding company or to acquire a bank or bank holding company. The facts that are considered in acting on the applications are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

Each application is available for immediate inspection at the Federal Reserve Bank indicated. Once the application has been accepted for processing, it will also be available for inspection at the offices of the Board of Governors. Interested persons may express their views in writing to the Reserve Bank or to the offices of the Board of Governors. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Unless otherwise noted, comments regarding each of these applications must be received not later than February 13, 1985.

A. **Federal Reserve Bank of Richmond** (Lloyd W. Bostian, Jr., Vice President) 701 East Byrd Street, Richmond, Virginia 23261:

1. *Intermountain Bancshares, Inc.,* Charleston, West Virginia; to acquire 100 percent of the voting shares of the successor by merger to Half Dollar Trust and Savings Bank, Wheeling, West Virginia.

B. *Federal Reserve Bank of Chicago* (Franklin D. Dreyer, Vice President) 230 South LaSalle Street, Chicago, Illinois 60690:

1. *ANB Corporation,* Muncie, Indiana; to become a bank holding company by acquiring 100 percent of the voting shares of American National Bank and Trust Company, Muncie, Indiana.

2. *FM Bancorp, Inc.,* Paxton, Illinois; to become a bank holding company by acquiring 100 percent of the voting shares of Farmers-Merchant National Bank of Paxton, Paxton, Illinois.

3. *Metro Bancorporation,* Waterloo, Iowa; to acquire 100 percent of the voting shares of Hudson State Bank, Hudson, Iowa.

C. **Federal Reserve Bank of St. Louis** (Delmer P. Weisz, Vice President) 411 Locust Street, St. Louis, Missouri 63166:

1. *Liberty United Bancorp, Inc.,* Louisville, Kentucky; to acquire indirectly through its wholly-owned subsidiary and proposed one bank holding company, 100 percent of the voting shares of Citizens State Bank, Owensboro, Kentucky.

D. **Federal Reserve Bank of Kansas City** (Thomas M. Hoenig, Vice President) 925 Grand Avenue, Kansas City, Missouri 64198:

1. *Brookside Bancshares, Inc.,* Tulsa, Oklahoma; to become a bank holding company by acquiring 81 percent of the voting shares of Brookside State Bank, Tulsa, Oklahoma.

Board of Governors of the Federal Reserve System, January 16, 1985.

James McAfee,

Associate Secretary of the Board.

[FR Doc. 85-1699 Filed 1-22-85; 8:45 am]

BILLING CODE 6210-01-M

Westbrook Bancshares, Inc., et al.; Applications To Engage de Novo in Permissible Nonbanking Activities

The companies listed in this notice have filed an application under § 225.23(a)(1) of the Board's Regulation Y (12 CFR 225.23(a)(1)) for the Board's approval under section 4(c)(8) of the Bank Holding Company Act (12 U.S.C. 1843(c)(8)) and § 225.21(a) of Regulation Y (12 CFR 225.21(a)) to commence or to engage *de novo*, either directly or through a subsidiary, in a nonbanking activity that is listed in § 225.25 of Regulation Y as closely related to banking and permissible for bank holding companies. Unless otherwise noted, such activities will be conducted throughout the United States.

Each application is available for immediate inspection at the Federal Reserve Bank indicated. Once the application has been accepted for processing, it will also be available for inspection at the offices of the Board of Governors. Interested persons may express their views in writing on the question whether consummation of the proposal can "reasonably be expected to produce benefits to the public, such as greater convenience, increased competition, or gains in efficiency, that outweigh possible adverse effects, such as undue concentration of resources, decreased or unfair competition, conflicts of interests, or unsound banking practices." Any request for a hearing on this question must be accompanied by a statement of the reasons a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute, summarizing the evidence that would be presented at a hearing, and indicating how the party commenting would be aggrieved by approval of the proposal.

Unless otherwise noted, comments regarding the applications must be received at the Reserve Bank indicated or the offices of the Board of Governors not later than February 12, 1985.

A. **Federal Reserve Bank of Chicago** (Franklin D. Dreyer, Vice President) 230 South LaSalle Street, Chicago, Illinois 60690:

1. *Westbrook Bancshares, Inc.,* Westchester, Illinois; to engage *de novo* through its subsidiary, West Brook Mortgage Corp., Westchester, Illinois, as principal or agent in mortgage financing activities in primary or secondary markets. The mortgages will be funded with nonrecourse, prior take out commitments and will be primarily residential.

B. **Board of Governors of the Federal Reserve System** (William W. Wiles, Secretary) Washington, D.C. 20551:

1. *Independent Bankers Financial Corporation,* Dallas, Texas; to enter through its subsidiary, Independent Brokerage Corporation of America, Inc., into a joint venture, Garvin Independent Brokers, New York, for the purpose of providing brokerage services to municipal bond dealers including municipal bond brokers and banks. These municipal bond brokerage services will be restricted to buying and selling municipal securities solely for the account of customers, and will not include dealing, underwriting, investment advice or research services. These activities will be conducted from offices in New York, New York and Dallas, Texas. This application may be inspected at the Federal Reserve Bank of Dallas.

Board of Governors of the Federal Reserve System, January 16, 1985.

James McAfee,

Associate Secretary of the Board.

[FR Doc. 85-1700 Filed 1-22-85; 8:45 am]

BILLING CODE 6210-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 81C-0353]

Colgate-Palmolive Co.; Withdrawal of Color Additive Petition

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the withdrawal without prejudice of the petition (CAP OCO149) that proposed to amend the color additive regulations to provide for the safe use of External D&C Yellow No. 5 as a color additive in drug and cosmetic toilet soaps.

FOR FURTHER INFORMATION CONTACT: Julia L. Ho, Center for Food Safety and Applied Nutrition (HFF-334), Food and Drug Administration, 200 C Street SW., Washington, DC 20204, 202-472-5690.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 4, 1981 (46 FR 59311), FDA published notice that it had filed a petition (CAP OCO149) from the Colgate-Palmolive Co., 300 Park Ave., New York, NY 10022, that proposed to amend Part 71 (21 CFR Part 74) to provide for the safe use of External D&C Yellow No. 5 as a color additive in drug and cosmetic toilet soaps. Colgate-Palmolive Co. has now withdrawn the petition without prejudice to a future filing (21 CFR 71.6).

Dated: January 11, 1985.

Richard J. Ronk,

Acting Director, Center for Food Safety and Applied Nutrition.

[FR Doc. 85-1708 Filed 1-22-85; 8:45 am]

BILLING CODE 4160-01-M

[Docket No. 84G-0392]

MULTI-KEM Corp.; Filing of Petition for Affirmation of GRAS Status

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that MULTI-KEM Corp. has filed a petition proposing affirmation that magnesium alginate is generally recognized as safe (GRAS) as a direct human food ingredient.

DATE: March 25, 1985.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Susan Thompson, Center for Food Safety and Applied Nutrition (HFF-335), Food and Drug Administation, 200 C Street SW., Washington, DC 20204, 202-426-9463.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5), 72 Stat. 1786 (21 U.S.C. 348(b)(5))) and the regulations for affirmation of GRAS status in § 170.35 (21 CFR 170.35), notice is given that a petiton (GRASP 4GO294) has been filed by MULTI-KEM Corp., 553 Broad Ave., Ridgefield, NJ 07657, proposing affirmation that magnesium alginate is generally recognized as safe (GRAS) as a direct human food ingredient .

The petition has been placed on display at the Dockets Management Branch (address above).

Any petition that meets the format requirements outlined in § 170.35 is filed by the agency. There is no prefiling review of the adequacy of data to support a GRAS conclusion. Thus, the filing of a petition for GRAS affirmation should not be interpreted as preliminary indication of suitability for affirmation.

Interested persons may, on or before March 25, 1985, review the petition and/or file comments (two copies, identified with the docket number found in brackets in the heading of this document) with the Dockets Management Branch (address above). Comments should include any available information that would be helpful in determining whether the substance is, or is not, GRAS. A copy of the petition and received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: January 11, 1985.

Richard J. Ronk,

Acting Director, Center for Food Safety and Applied Nutrition.

[FR Doc. 85-1707 Filed 1-22-85; 8:45 am]

BILLING CODE 4160-01-M

Medical Radiation; Advisory Committee; Meeting

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This notice announces a forthcoming meting of a public advisory committee of the Food and Drug Administration (FDA). This notice also summarizes the procedures for the meetings and methods by which interested persons may participate in open public hearings before FDA's advisory committees.

MEETING: The following advisory committee meeting is announced:

Medical Radiation Advisory Committee

Date, time, and place. February 11 and 12, 8:30 a.m., Rm. T-416, 12720 Twinbrook Parkway, Rockville, MD.

Type of meeting and executive secretary. Open public hearing, February 11, 8:30 a.m. to 9:30 a.m.; open committee discussion, February 11, 9:30 a.m. to 4:30 p.m., February 12, 8:30 a.m. to 3 p.m.; Donald R. Hamilton, Center for Devices and Radiological Health (HFZ-240), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-2436.

General function of the committee. The committee advises the Commissioner of Food and Drugs in the formulation of policy and development of a coordinated program relating to medical application of radiation directed at obtaining the maximum diagnostic information and therapeutic benfits per unit of radiation exposure through optimum utilization of professional and technical resources and radiation related equipment.

Agenda—Open public hearing. Interested persons may present data, information, or views orally or in writing, on issues pending before the committee. Those desiring to make formal presentations should notify the executive secretary before January 28, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time required to make their comments.

Open committee discussion. The committee will discuss its role in providing a link to the clinical environment, computer software involved in medical radiation, diagnostic imaging topics, and other topics affecting the safe and effective use of medical radiation. A complete agenda will be available on request after January 28.

FDA public advisory committee meetings may have as many as four separable portions: (1) An open public hearing, (2) an open committee discussion, (3) a closed presentation of data, and (4) a closed committee deliberation. Every advisory committee meeting shall have an open public hearing portion. Whether or not it also includes any of the other three portions will depend upon the specific meeting

involved. There are no closed portions for the meetings announced in this notice. The dates and times reserved for the open portions of each committee are listed above.

The open public hearing portion of each meeting shall be at least 1 hour long unless public participation does not last that long. It is emphasized, however, that the 1 hour time limit for an open public hearing represents a minimum rather than a maximum time for public participation, and an open public hearing may last for whatever longer period the committee chairman determines will facilitate the committee's work.

Public hearings are subject to FDA's guideline concerning the policy and procedures for electronic media coverage of FDA's public administrative procedings. This guideline was published in the **Federal Register** of April 13, 1984 (49 FR 14723). These procedures are primarily intended to expedite media access to FDA's public proceedings, including hearings before a public advisory committee conducted pursuant to Part 14 of the agency's regulations. Under this guideline, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including the presentation of participants at a public hearing. Accordingly, all interested persons are directed to the guideline, as well as the **Federal Register** notice announcing issuance of the guideline, for a more complete explanation of the guideline's effect on public hearings.

Meetings of advisory committees shall be conducted, insofar as is practical, in accordance with the agenda published in this **Federal Register** notice. Changes in the agenda will be announced at the beginning of the open portion of a meeting.

Any interested person who wishes to be assured of the right to make an oral presentation at the open public hearing portion of a meeting shall inform the contact person listed above, either orally or in writing, prior to the meeting. Any person attending the hearing who does not in advance of the meeting request an opportunity to speak will be allowed to make an oral presentation at the hearing's conclusion, if time permits, at the chairman's discretion.

Persons interested in specific agenda items to be discussed in open session may ascertain from the contact person the approximate time of discussion.

A list of committee members and summary minutes of meetings may be requested from the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, between the hours of 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under section 10(a) (1) and (2) of the Federal Advisory Committee Act (Pub. L. 92–463, 86 Stat. 770–776 (5 U.S.C. App. I)), and FDA's regulations (21 CFR Part 14) on advisory committees.

Dated: January 12, 1985.

Joseph P. Hile,

Associate Commissioner for Regulatory Affairs.

[FR Doc. 85–1710 Filed 1–22–85; 8:45 am]

BILLING CODE 4160–01–M

Advisory Committee; Ophthalmic Devices Panel; Meeting

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). This notice also summarizes the procedures for the meetings and methods by which interested persons may participate in open public hearings before FDA's advisory committees.

Meeting: The following advisory committee meeting is announced:

Ophthalmic Devices Panel

Date, time, and place. February 7 and 8, 9 a.m., Auditorium, 200 Independence Avenue SW., Washington, DC.

Type of meeting and executive secretary. Open public hearing, February 7, 9 a.m. to 10 a.m.; open committee discussion, 10 a.m. to 1 p.m.; closed committee deliberations, 2 p.m. to 5 p.m.; open public hearing, February 8, 9 a.m. to 10 a.m.; open committee discussion, 10 a.m. to 1 p.m; closed committee deliberations, 2 p.m. to 3 p.m.; open committee discussion, 3 p.m. to 5 p.m.; George C. Murray, Center for Devices and Radiological Health (HFZ–460), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301–427–7940.

General function of committee. The committee reviews and evaluates available data on the safety and effectiveness of devices currently in use and makes recommendations for their regulation. The committee also reviews data on new devices and makes recommendations regarding their safety and effectiveness and their suitability for marketing.

Agenda—Open public hearing. Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Those desiring to make formal presentations should notify the executive secretary before February 4, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time required to make their comments.

Open committee discussion. On February 7, the committee will discuss general issues relating to approvals of premarket approval applications (PMA's) for intraocular lenses (IOL's) and neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers, and may discuss specific PMA's for these devices. The committee will discuss the ongoing pediatric IOL investigations (current protocols, clinical results, and current usage of IOL's in children). Investigational sponsors, surgeons, and other interested persons may present data, information, or views orally; supporting documentation and confidential data may be submitted in writing for committee and FDA use. Those desiring to make presentations should proceed as described above. If discussion of all pertinent IOL or Nd:YAG laser issues is not completed, discussion will be continued the following day. On February 8, the committee will discuss PMA's for contact lenses and other ophthalmic devices and requirements for PMA approval. Comments received on the draft Testing Guidelines for Class III Contact Lenses, distributed at the October 23 meeting, will be discussed. Testing protocols and labeling for contact lenses and solutions will also be discussed.

Closed committee deliberations. On February 7, the committee will conduct reviews of PMA's for IOL's and Nd:YAG lasers. On February 8, the committee may discuss trade secret or confidential commercial information relevant to PMA's for contact lens or other ophthalmic devices. These portions of the meeting will be closed to permit discussion of this information (5 U.S.C. 552b(c)(4)).

Each public advisory committee meeting listed above may have as many as four separable portions: (1) An open public hearing, (2) an open committee discussion, (3) a closed presentation of data, and (4) a closed committee deliberation. Every advisory committee meeting shall have an open public hearing portion. Whether or not it also includes any of the other three portions will depend upon the specific meeting involved. The dates and times reserved

for the separate portions of each committee meeting are listed above.

The open public hearing portion of each meeting shall be at least 1 hour long unless public participation does not last that long. It is emphasized, however, that the 1 hour time limit for an open public hearing represents a minimum rather than a maximum time for public participation, and an open public hearing may last for whatever longer period the committee chairman determines will facilitate the committee's work.

Public hearings are subject to FDA's guideline concering the policy and procedures for electronic media coverage of FDA's public administrative proceedings. This guideline was published in the **Federal Register** of April 13, 1984 (49 FR 14723). These procedures are primarily intended to expedite media access to FDA's public proceedings, including hearings before a public advisory committee conducted pursuant to Part 14 of the agency's regulations. Under this guideline, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including the presentation of participants at a public hearing. Accordingly, all interested persons are directed to the guideline, as well as the **Federal Register** notice announcing issuance of the guideline, for a more complete explanation of the guideline's effect on public hearings.

Meetings of advisory committees shall be conducted, insofar as is practical, in accordance with the agenda published in this **Federal Register** notice. Changes in the agenda will be announced at the beginning of the open portion of a meeting.

Any interested person who wishes to be assured of the right to make an oral presentation at the open public hearing portion of a meeting shall inform the contact person listed above, either orally or in writing, prior to the meeting. Any person attending the hearing who does not in advance of the meeting request an opportunity to speak will be allowed to make an oral presentation at the hearing's conclusion, if time permits, at the chairman's discretion.

Persons interested in specific agenda items to be discussed in open session may ascertain from the contact person the approximate time of discussion.

A list of committee members and summary minutes of meetings may be requested from the Dockets Management Branch (HFA–305), Rm. 4–62, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

The Commissioner, with the concurrence of the Chief Counsel, has determined for the reasons stated that those portions of the advisory committee meetings so designated in this notice shall be closed. The Federal Advisory Committtee Act (FACA), as amended by the Government in the Sunshine Act (Pub. L. 94–409), permits such closed advisory committee meetings in certain circumstances. Those portions of a meeting designated as closed, however, shall be closed for the shortest possible time, consistent with the intent of the cited statutes.

The FACA, as amended, provides that a portion of a meeting may be closed where the matter for discussion involves a trade secret; commercial or financial information that is privileged or confidential; information of a personal nature, disclosure of which would be a clearly unwarranted invasion of personal privacy; investigatory files compiled for law enforcement purposes; information the premature disclosure of which would be likely to significantly frustrate implementation of a proposed agency action; and information in certain other instances not generally relevant to FDA matters.

Examples of portions of FDA advisory committee meetings that ordinarily may be closed, where necessary and in accordance with FACA criteria, include the review, discussion, and evaluation of drafts of regulations or guidelines or similar preexisting internal agency documents, but only if their premature disclosure is likely to significantly frustrate implementation of proposed agency action; review of trade secrets and confidential commercial or financial information submitted to the agency; consideration of matters involving investigatory files compiled for law enforcement purposes; and review of matters, such as personnel records or individual patient records, where disclosure would constitute a clearly unwarranted invasion of personal privacy.

Examples of portions of FDA advisory committee meetings that ordinarily shall not be closed include the review, discussion, and evaluation of general preclinical and clinical test protocols and procedures for a class of drugs or devices; consideration of labeling requirements for a class of marketed drugs or devices; review of data and information on specific investigational or marketed drugs and devices that have previously been made public; presentation of any other data or information that is not exempt from public disclosure pursuant to the FACA, as amended; and notably deliberative sessions to formulate advice and recommendations to the agency on matters that do not independently justify closing.

This notice is issued under section 10(a) (1) and (2) of the Federal Advisory Committee Act (Pub. L. 92–463, 86 Stat. 770–776 (5 U.S.C. App. I)], and FDA's regulations (21 CFR Part 14) on advisory committees.

Dated: January 15, 1985.

Mark Novitch,

Acting Commissioner of Food and Drugs.

[FR Doc. 85–1709 Filed 1–22–85; 8:45 am]

BILLING CODE 4160–01–M

Health Resources and Services Administration

National Council on Health Planning and Development; Rechartering

Pursuant to the Federal Advisory Committee Act, Pub. L. 92–463, (5 U.S.C. Appendix I), the Health Resources and Services Administration announces the rechartering by the Secretary, HHS, on January 4, 1985, of the following advisory Council:

Council and Termination Date

National Council on Health Planning and Development, Continuing

Authority for this Council is continuing and a Charter will be filed no later than January 4, 1987, in accordance with section 14(b)(2) of Pub. L. 92–463.

Dated: January 16, 1985.

Jackie E. Baum,

Advisory Committee Management Officer, HRSA.

[FR Doc. 85–1705 Filed 1–22–85; 8:45 am]

BILLING CODE 4160–15–M

Advisory Committee; Establishment of Organ Transplantation Task Force; Correction

In **Federal Register** Document 85–789 appearing at page 1943 in the issue for Monday, January 14, 1985, the Task Force on Organ Transplantation was established by the Secretary, HHS, on January 14, 1985. All other information is correct as appears.

Dated: January 16, 1985.

Jackie E. Baum,

Advisory Committee Management Officer, HRSA.

[FR Doc. 85–1706 Filed 1–22–85; 8:45 am]

BILLING CODE 4160–15–M

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

[M59847; 5-00254]

Montana; Modification of Notice of Realty Action; Exchange

AGENCY: Bureau of Land Management, Butte District Office, Interior.

ACTION: Modification of Notice of Realty Action M59847, Exchange of Public and Private Lands in Lewis and Clark, Jefferson, Broadwater, Gallatin, Park, and Sweet Grass Counties.

SUMMARY: This Notice modifies the original Notice of Realty Action for M59847 published on December 12, 1984 (49 FR 48391). The following described tract is included with those lands identified under parcel number J-9: T. 8 N., R. 4 W., P.M.M., Section 15, SE¼SW¼, 40 acres.

Dated: January 14, 1985.

Jack A. McIntosh,

District Manager Butte District.

[FR Doc. 85-1676 Filed 1-22-85; 8:45 am]

BILLING CODE 4310-DN-M

[SAC 605 WR, CA 7003 WR, CA 7006 WR, CA 7009 WR, CA 7011 WR, CA 7015 WR, CA 7016 WR, CA 7018 WR, CA 7019 WR, CA 7020 WR; 4-19952-ILM]

Proposed Continuation of Withdrawals; California

January 14, 1985

AGENCY: Bureau of Land Management, Interior.

ACTION: Notice.

SUMMARY: The Bureau of Reclamation, Mid-Pacific Region, proposes that 10 land withdrawals aggregating approximately 2,090 acres for the Keswick Reservoir Area of the Central Valley Project continue for additional periods of 20 and 50 years. The lands will remains closed to surface entry and mining, but have been and will remain open to mineral leasing.

DATE: Comments should be received by April 23, 1985.

ADDRESS: Comments should be sent to: Chief, Branch of Lands and Minerals Operations Bureau of Land Management, California State Office, 2800 Cottage Way (Room E-2841), Sacramento, CA 95825.

FOR FURTHER INFORMATION CONTACT: Sonia I. Santillan, California State Office (916) 484-4431.

SUPPLEMENTARY INFORMATION: The Bureau of Reclamation proposes that 10 existing withdrawals of land be continued for periods of 20 and 50 years, pursuant to the provisions of the Section 204 of the Federal Land Policy and Management Act of 1976, 90 Stat. 2751; 43 U.S.C. 1714. The withdrawals are described as follows:

Mount Diablo Meridian

SAC 605 WR

Public Land Order 4326 of November 29, 1967

T. 32 N., R. 5 W.,
Sec. 4, lot 22 and lot 52 (MS 3229 Mammoth Millsite).

The area described contains 9.00 acres in Shasta County.

CA 7003 WR

Secretarial Order of April 20, 1936

T. 32 N., R. 5 W.,
Sec. 4, N½ lot 21, SE¼ lot 21, W½ lot 26, SE¼ lot 28, E½ lot 29, and W½ lot 31;
Sec. 8, lots 14 and 15, and NW¼ lot 22;
9, S½ lot 3;
Sec. 17, NE¼ lot 18, S½ lot 18, lots 20 and 23.
T. 33 N., R. 5 W.,
Sec. 21, lots 2, 3, and 4;
Sec. 32, SE¼ lot 8, E½ lot 17, W½ lot 18, and E½ lot 20.

The areas described aggregate 353.68 acres in Shasta County.

CA 7006 WR

Secretarial Order of July 29, 1936

T. 32 N., 5 W.,
Sec. 4, S½ lot 20, SW¼ lot 21, lot 27, N½ lot 28, and lot 30;
Sec. 5, lot 5;
Sec. 8, NE¼ lot 22, and S½ lot 22;
Sec. 9, N½ lot 3, E½ lot 4, lot 5, W½ lot 6, and lot 12;
Sec. 17, NW ¼ lot 18.
T. 33N., R. 5 W.,
Sec. 32, lots 5, 9, 11, 12, 19, W½ lot 17, E½ lot 18, W½ lot 20, N½ lot 8, and SW¼ lot 8.

The areas described aggregate 397.60 acres in Shasta County.

CA 7009 WR

Secretarial Order of February 6, 1941, as amended

T. 32N., R. 5 W.,
Sec. 21, lots 2 and 3.

The area described contains 26.33 acres in Shasta County.

CA 7011 WR

Secretarial Order of May 12, 1945

T. 32 N., R. 5 W.,
Sec. 16, lot 1.

The area described contains 24.27 acres in Shasta County.

CA 7015 WR

Bureau of Land Management Order of February 27, 1952

T. 32 N., R. 5 W.,
Sec. 7, lot 33;
Sec. 18, lot 12, 13, 14, and NW¼NE¼.

The areas described aggregate 108.20 acres in Shasta County.

CA 7016 WR

Bureau of Land of Management Order of October 21, 1955, as amended

T. 32 N., R. 5 W.,
Sec. 7, lot 25 and 26;
Sec. 17, lot 17;
Sec. 18, lot 1 to 11 incl., and NE¼NW¼.
T. 33 N., R. 5 W.,
Sec. 31, lots 2 to 5 incl.,
T. 32N., R. 6 W.,
Sec. 13, lot 1.

The areas described aggregate 379.18 acres in Shasta County.

CA 7018 WR

Bureau of Land Management Order of December 10, 1946

T. 32 N., R. 5 W.,
Sec. 5, lot 6;
Sec. 6, lots 14, 15, 16, 17, 19, and 21

The areas described aggregate 214.39 acres in Shasta County.

CA 7019 WR

Secretarial Order of July 7, 1936

T. 32 N., R. 5 W.,
Sec. 4, N½ lot 20, lot 23, D½ lot 26, SW¼ lot 28, W½ lot 29, and E½ lot 31;
Sec. 8, lots 12 and 13;
Sec. 9, lot 2, W½ lot 4, E½ lot 6, Lot 7, lot 10, and lot 11;
Sec. 20, lots 8, 9, 10, and 14.
T. 33 N., R. 5 W.,
Sec. 32, lots 7, 13, and 14.

The areas described aggregate 552.42 acres in Shasta County.

CA 7020 WR

Secretarial Order of July 29, 1936

T. 32 N., R. 5 W.,
Sec.1 7, lot 19.

The area described contains 24.22 acrs in Shasta County.

The purpose of the withdrawal is to protect lands around the Keswick Reservoir area of the Central Valley Project. The withdrawals segregate the lands from operations of the public land laws generally, including the mining laws. No change is proposed in the purpose or segregative effect of the withdrawals.

For a period of 90 days from the date of publication of this notice, all persons who wish to submit comments in connection with the proposed withdrawal continuation may present their views in writing to the Chief, Branch of Lands and Minerals Operations, in the California State Office.

The authorized Office of the Bureau of Land Management will undertake such investigations as are necessary to determine the existing and potential demand for the land and its resources. A report will also be prepared for consideration by the Secretary of the Interior, the President, and Congress, who will determine whether or not the

withdrawals will be continued and, if so, for how long. The final determination on the continuation of the withdrawals will be published in the Federal Register. The existing withdrawals will continue until such final determination is made.

Sharon N. Janis,

Chief, Branch of Lands Minerals Operations.

[FR Doc. 85-1669 Filed 1-22-85; 8:45 am]

BILLING CODE 4310-84-M

Wyoming; Availability of the Amendment to the Hanna Basin Management Framework Plan and Environmental Assessment

AGENCY: Bureau of Land Management, Interior, Wyoming State Office, Cheyenne, Wyoming, and the Rawlins District Office, Rawlins, Wyoming.

ACTION: Notice of availability of the amendment to the Hanna Basin Management Framework Plan and Environmental Assessment.

SUMMARY: As stated in the final environmental assessment (EA), the decision is to amend the Hanna Basin land-use plan to remove the 2,000-foot scenic buffer zone around Seminoe Reservoir and to make the Medicine Bow emergency lease application area acceptable for coal development and further leasing consideration. The lease area is located northwest of the city of Rawlins, Wyoming, and east of Seminoe Reservoir. The multiple use analysis and environmental assessment indicate there would be no significant adverse impacts to this area if it were mined under the mitigative measures identified in the EA. If the area were not mined, a significant amount of federal and private coal would be bypassed because it would not be practical or economically feasible to return and mine bypassed coal at a latter date. This involves approximately 13 million tons of recoverable federal coal and 5 million tons of privately owned coal, and indirectly affects another 2.5 million tons of leased federal coal. All comments received during the public review period for the draft amendment were considered.

DATES: As of the date of this publication, the final amendment and KA document is available. A 30-day protest period begins with publication of this notice. Protests should be received by the Director of the Bureau of Land Management no later than 30 days from the date of this publication.

ADDRESSES: Protests are to be sent to the Director of the Bureau of Land Management, Department of the Interior, Washington, D.C. 20240. Any other comments on the final EA should be sent to the Rawlins District Manager, Bureau of Land Management, Box 670, Rawlins, WY 82301. This document is available for review at the Rawlins District Office, 1300 3rd Street, Rawlins, Wyoming.

FOR FURTHER INFORMATION CONTACT: Gene Kolkman, Rawlins District Office, Box 670, Rawlins, Wyoming 82301, Telephone (307) 324-7171.

Paul D. Leonard,

Associate State Director.

[FR Doc. 85-1841 Filed 1-22-85; 8:45 am]

BILLING CODE 4310-22-M

National Park Service

National Register of Historic Places; Pending Nominations

Nominations for the following properties being considered for listing in the National Register were received by the National Park Service before January 12, 1985. Pursuant to § 60.13 of 36 CFR Part 60 written comments concerning the significance of these properties under the National Register criteria for evaluation may be forwarded to the National Register, National Park Service, U.S. Department of the Interior, Washington, DC 20243. Written comments should be submitted by February 7, 1984.

Carol D. Shull,

Chief of Registration, National Register.

ARIZONA

Maricopa County

Phoenix, *Douglas, Lewis, House,* 815 Orangewood Ave.

COLORADO

El Paso County

Coloado Springs, *North Weber Street-Wahsatch Avenue Historic Residential District,* N. Weber St. between Boudler and Del Norte St., and N. Wahsatch Ave. between St. Vrain and Columbia St.

Larimer County

Fort Collins, *Opera House Block/Central Block Building,* 117-131 N. College Ave.

Pueblo County

Pueblo, *Carlile, James N., House,* 44 Carlile Pl.
Pueblo, *Duke, Nathaniel W., House,* 1409 Craig St.
Pueblo, *First Congregation Church,* 225 W. Evans
Pueblo, *Pryor, Frank, House,* 1325 Greenwood St.
Pueblo, *Stickney, Charles H., House,* 101 E. Orman Ave.

MAINE

Franklin County

Temple, *Temple Intervale School,* Temple Intervale

Hancock County

Brooklin vicinity, *Flye Point—2*

Lincoln County

Damariscotta, *Huston House,* Bristol Rd.
South Bristol, *Means, Emily, House,* Birch Island

Sagadahoc County

Bath, *Merritt, Captain, House,* 619 High St.
Phippsburg, *Cold Spring Farm,* Off Fiddler's Reach Rd.

York County

Newfield, *Newfield (Willowbrook) Historic District,* Elm St.

NEW MEXICO

San Juan County

Aztec, *Abrams, H. D., House (Aztec New Mexico Historic MRA),* 403 N. Church
Aztec, *American Hotel (Aztec New Mexico Historic MRA),* 300 S. Main
Aztec, *Austin-McDonald (Koogler) House (Aztec New Mexico Historic MRA),501 Rio Grande*
Aztec, *Aztec Main Street Historic District (Aztec New Mexico Historic MRA),* Bounded by Main E., Chuska S., alley between Park and Main W., and Chaco N.
Aztec, *Aztec Motor Company Building (Aztec New Mexico Historic MRA),* 301 S. Main
Aztec, *Ball, D.C., House (Aztec New Mexico Historic MRA),* 300 San Juan
Aztec, *Building at 202 Park Avenue (Aztec New Mexico Historic MRA),* 202 Park Ave.
Aztec, *Building at 500 White Avenue (Aztec New Mexico Historic MRA),* 500 White Ave.
Aztec, *Church Avenue-Lovers Lane Historic District (Aztec New Mexico Historic MRA),* Bounded by Rio Grande E., Zia S., Park W. and NM 550
Aztec, *Daws-Keys House (Aztec New Mexico Historic MRA),* 421 N. Church
Aztec, *Denver and Rio Grande Western Railway Depot (Aztec New Mexico Historic MRA),* 314 Rio Grande
Aztec, *Engleman-Thomas Building (Old Post Office) (Aztec New Mexico Historic MRA),* 200 S. Main
Aztec, *Lower Animas Ditch (Aztec New Mexico Historic MRA),* Lower Animas Ditch from Church Ave. to Lovers Lane Historic District
Aztec, *McCoy, Harvey, House (Aztec New Mexico Historic MRA),* 725 Pioneer
Aztec, *McCoy-Maddox (Spargo) House (Aztec New Mexico Historic MRA),* NW corner of Maddox and NE Aztec Blvd.
Aztec, *McGee House (Aztec New Mexico Historic MRA),* 501 Sabena St.

NORTH DAKOTA

Walsh County

Grafton, *Elmwood,* P.O. Box 654

WYOMING

Albany County

Bosler vicinity, *DOE Bridge over Laramie River (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CNA–740

Big Horn County

Hyattville vicinity, *EJP County Line Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN9–60
Lovell vicinity, *EJZ Bridge over Shoshone River (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN9–111
Manderson vicinity, *Rairden Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, S. of Big Horn CR CN9–30
Shell vicinity, *EJE Bridge over Shell Creek (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN9–57

Carbon County

Elk Mountain vicinity, *DFU Elk Mountain Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR 120–1
Encampment vicinity, *DML-Butler Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN6–203
Saratoga vicinity, *DMJ Pick Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN6–508 (Pick Bridge Rd.)

Crook County

Hulett vicinity, *DXN Bridge over Missouri River (Vehicular Truss and Arch Bridges in Wyoming TR)*, Crook CR 18–200

Fremont County

Dubois vicinity, *ELS Bridge over Big Wind River (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN10–21
Ethete vicinity, *BMU Bridge over Wind River (Vehicular Truss and Arch Bridges in Wyoming TR)*, WY 132
Morton vicinity, *ELY Wind River Diversion Dam Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN10–24

Hot Springs County

Thermopolis vicinity, *CQA Four Mile Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, WY 173
Thermopolis vicinity, *EFP Bridge over Owl Creek (Vehicular Truss and Arch Bridges in Wyoming TR), CR CN15–28*

Johnson County

Buffalo vicinity, *EDL Pelous Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN16–40
Kaycee vicinity, *AJX Bridge over South Fork and Powder River (Vehicular Truss and Arch Bridges in Wyoming TR)*, I–25 W. Service Rd. (old hwy 87)
Sussex vicinity *EDZ Irigary Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN16–254

Natrona County

Bessemer Bend, *DUX Bessemer Bend Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN1–58

Niobrara County

Riverview vicinity, *DSD Bridge over Cheyenne River (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN14–46

Park County

Cody vicinity, *Hayden arch Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, Old U.S. 14/16 (Cody Yellowstone Hwy)

Platte County

Wheatland vicinity, *EWZ Bridge over East Channell of Laramie River (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN8–204

Sheridan County

Arvada vicinity, *CKW Bridge over Powder River (Vehicular Truss and Arch Bridges in Wyoming TR)*, U.S. 14/16
Arvada vicinity, *EAU Arvada Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN3–38
Leiter vicinity, *EBF Bridge over Powder River (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN3–269
Monarch vicinity, *ECR Kooi Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN3–93
Sheridan vicinity, *ECA Bridge over Big Goose Creek (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN3–93

Sublette County

Boulder vicinity, *DDZ Bridge over New Fork River (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR 136
Daniel vicinity, *ENP Bridge over Green River (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN23–145

Sweetwater County

Fontenelle, *ETD Bridge over Green River (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN4–8SS
Green River vicinity, *ETR Big Island Bridge (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN4–4

Uinta County

Fort Bridger vicinity, *ERT Bridge over Black's Fork (Vehicular Truss and Arch Bridges in Wyoming TR)*, CR CN19–217.

[FR Doc. 85–1729 Filed 1–22–85; 8:45 am]
BILLING CODE 4310–76–M

INTERNATIONAL TRADE COMMISSION

[332–205]

Conditions of Competition in Air and Surface Cargo Transportation Services Between Japan and the United States

AGENCY: United States International Trade Commission.

ACTION: Institution of an investigation under section 332(g) of the Tariff Act of 1930 (19 U.S.C. 1332(g)) and scheduling of a hearing in connection therewith.

EFFECTIVE DATE: January 11, 1985.

FOR FURTHER INFORMATION CONTACT: Dr. Paul Golding, Research Division, Office of Economics, U.S. International Trade Commission, Washington, D.C. 20436, telephone 202–523–1542.

Background

At the direction of the President, the U.S. Trade Representative (USTR) on December 12, 1984, requested that the Commission institute an investigation under section 332(g) of the Tariff Act of 1930 to study and report on current and prospective conditions of competition in cargo transport services between the United States and Japan. As requested by USTR, the Commission's report, to the extent possible, will include an examination and assessment of Japanese Government and national industry policies, regulations, and activities which have a significant effect on trade conditions in cargo transportation services, and the report will include an asessment of the real economic impact caused by potentially lost U.S. export opportunities, particularly in transportation services, as a consequence of such practices and conditions. The USTR requested that the Commission complete its study and report the results thereof not later than 6 months after receipt of the request (i.e. by June 12, 1985).

Public Hearing

A public hearing in connection with the investigation will be held at the International Trade Commission in Washington, D.C. on April 9, 1985 at 10 A.M. All interested persons shall have the right to appear by counsel or in person, to present information and to be heard. Requests to appear at the public hearing should be filed with the Secretary, U.S. International Trade Commission, 701 E Street NW., Washington, D.C. 20436, not later than noon, March 29, 1985.

Written Submissions

In lieu of, or in addition to, appearances at the public hearing, interested persons are invited to submit written statements concerning the investigation. Commercial or financial information which a submitter desires the Commission to treat as confidential must be submitted on separate sheets of paper, each clearly marked "Confidential Business Information" at the top. All submissions requesting confidential treatment must conform with the requirements of § 201.6 of the Commission's rules of practice and procedure (19 CFR 201.6). All written submissions, except for confidential business information, will be made available for inspection by interested persons. To be ensured of consideration by the Commission, written statements

should be submitted at the earliest practicable date, but not later than April 19, 1985. All submissions should be addressed to the Secretary at the Commission's office in Washington, D.C.

Issued: January 11, 1985.

By order of the Commission.

Kenneth R. Mason,

Secretary.

[FR Doc. 85-1654 Filed 1-22-85; 8:45 am]

BILLING CODE 7020-02-M

[332-204]

Competitive Assessment of the U.S. Commuter and Business Aircraft Industries

AGENCY: United States International Trade Commission.

ACTION: Institution of an investigation under section 332(b) of the Tariff Act of 1930 (19 U.S.C. 1332(b) for the purpose of presenting information on the competitiveness of the U.S. commuter and busines aircraft industries.

EFFECTIVE DATE: January 9, 1985.

FOR FURTHER INFORMATION CONTACT: Ms. Deborah Ladomirak or Mr. Eric Nelson, Machinery and Equipment Division, Office of Industries, U.S. International Trade Commission, Washington, D.C. 20436 (telephone 202-523-0131 or 202-523-4585).

Background and Scope of Investigation

The Commission instituted the investigation on its own motion for the purpose of gathering information on the competitive position of the U.S. and foreign commuter and business aircraft industries. The study will assess the impact of the growing competition from imports on the U.S. commuter and business aircraft industries, explore the related development of further competition in overseas markets, and examine the steps taken in response to this increased competition.

Written Submissions

Interested persons are invited to submit written statements concerning the investigation. Written statements should be received by the close of business on July 25, 1985. Commercial or financial information which a submitter desires the Commission to treat as confidential must be submitted on separate sheets of paper, each clearly marked "Confidential Business Information" at the top. All submissions requesting confidential treatment must conform with the requirements of § 201.6 of the Commission's *Rules of Practice and Procedure* (19 CFR 201.6). All written submissions, except for confidential business information will be made available for inspection by interested persons. All submissions should be addressed to the Secretary, United States International Trade Commission, 701 E Street NW., Washington, D.C. 20436.

Issued: January 11, 1985.

By order of the Commission.

Kenneth R. Mason,

Secretary.

[FR Doc. 85-1653 Filed 1-22-85; 8:45 am]

BILLING CODE 7020-02-M

[Investigation No. 337-TA-207]

Certain Automotive Transmission Shifters; Initial Determination Terminating Respondents on the Basis of Settlement Agreement

AGENCY: U.S. International Trade Commission.

ACTION: Notice is hereby given that the Commission has received an initial determination from the presiding officer in the above-captioned investigation terminating the following respondents on the basis of a settlement agreement: Isuzu Motors Ltd.; American Isuzu Motors Inc. and Keihin Seimitsu Kogyo Co., Ltd.

SUPPLEMENTARY INFORMATION: This investigation is being conducted pursuant to section 337 of the Tariff Act of 1930 (19 U.S.C 1337). Under the Commission's rules, the presiding officer's initial determination will become the determination of the Commission thirty (30) days after the date of its service upon the parties, unless the Commission orders review of the initial determination. The initial determination in this matter was served upon the parties on January 16, 1985.

Copies of the initial determination, the settlement agreement, and all other nonconfidential documents filed in connection with this investigation are available for inspection during official business hours (8:45 a.m. to 5:15 p.m.) in the Office of the Secretary, U.S. International Trade Commission, 701 E Street NW., Washington, D.C. 20436, telephone 202-523-0161.

Written Comments

Interested persons may file written comments with the Commission concerning termination of the aforementioned respondents. The original and 14 copies of all such comments must be filed with the Secretary to the Commission, 701 E Street, NW., Washington, D.C. 20436, no later than 10 days after publication of this notice in the **Federal Register**.

Any person desiring to submit a document (or portion thereof) to the Commission in confidence must request confidential treatment. Such requests should be directed to the Secretary to the Commission and must include a full statement of the reasons why confidential treatment should be granted. The Commission will either accept the submission in confidence or return it.

FOR FURTHER INFORMATION CONTACT: Ruby J. Dionne, Office of the Secretary, U.S International Trade Commission, telephone 202-523-0176.

Issued: January 16, 1985.

By order of the Commission.

Kenneth R. Mason,

Secretary.

[FR Doc. 85-1650 Filed 1-22-85; 8:45 am]

BILLING CODE 7020-02-M

[Investigation No. 701-TA-218 (Final)]

Certain Cold-Rolled Carbon Steel Products From the Republic of Korea; Determination

On the basis of the record [1] developed in the subject investigation, the Commission determines,[2] pursuant to section 705(b) of the Tariff Act of 1930 (19 U.S.C. 1671d(b)), that an industry in the United States is materially injured or threatened with material injury [3] by reason of imports from the Republic of Korea (Korea) of cold-rolled carbon steel plates and sheets, provided for in item 607.83 of the Tariff Schedules of the United States, which have been found by the Department of Commerce to be subsidized by the Government of Korea.

Background

The Commission instituted this investigation effective September 18, 1984, following a preliminary determination by the Department of Commerce that imports of the subject carbon steel products from Korea were being subsidized within the meaning of section 701 of the Act (19 U.S.C. 1671). Notice of the institution of the-

[1] The record is defined in § 207.2(i) of the Commission's Rules of Practice and Procedure (19 CFR 207.2(i)).

[2] Vice Chairman Liebeler dissenting.

[3] Chairwoman Stern and Commissioner Rohr determine that an industry in the United States is threatened with material injury by reason of imports of the subject products from Korea. Accordingly, pursuant to section 705(b)(4) of the Act (19 U.S.C. 1671d(b)(4)), they further determine that they would not have found material injury but for any suspension of liquidation of entries of that merchandise. Commissioner Eckes and Commissioner Lodwick determine that an industry in the United States is materially injured by reason of imports of the subject products from Korea.

Commission's investigation and of a public hearing to be held in connection therewith was given by posting copies of the notice in the Office of the Secretary, U.S. International Trade Commission, Washington, DC, and by publishing it in the **Federal Register** on October 17, 1984 (49 FR 40676). A second notice, announcing a rescheduling of the hearing, was published in the **Federal Register** on November 30, 1984 (49 FR 47121). The hearing was held in Washington, DC, on December 13, 1984, and all persons who requested the opportunity were permitted to appear in person or by counsel.

The Commission transmitted its determination in this investigation to the Secretary of Commerce on January 15, 1985. The views of the Commission are contained in USITC Publication 1634 (January 1985), entitled "Certain Cold-Rolled Carbon Steel Products from the Republic of Korea: Determination of the Commission in Investigation No. 701–TA–218 (Final) Under the Tariff Act of 1930, Together With the Information Obtained in the Investigation."

Issued: January 15, 1985.

By Order of the Commission.

Kenneth R. Mason,

Secretary.

[FR Doc. 85–1649 Filed 1–22–85; 8:45 am]

BILLING CODE 7020–02–M

[Investigation No. 337–TA–213]

Certain Fluidized Bed Combustion Systems; Investigation

AGENCY: U.S. International Trade Commission.

ACTION: Institution of investigation pursuant to 19 U.S.C. 1337.

SUMMARY: Notice is hereby given that a complaint was filed with the U.S. International Trade Commission on December 14, 1984, under section 337 of the Tariff Act of 1930 (19 U.S.C. 1337), on behalf of Wormser Engineering, Inc., 225 Merrimac Street, P.O. Box 4007, Woburn, Massachusetts 01888. The complaint alleges unfair methods of competition and unfair acts in the importation of certain fluidized bed comubustion systems into the United States, or in their sale, by reason of alleged: (1) infringement of claims 1, 4, 5, and 8 of U.S. Letters Patent 4,279,205; (2) infringement of claims 1, 2, 4, and 5 of U.S. Letters Patent 4,303,023; (3) misappropriation of trade secrets; and (4) fraudulent inducement to enter into a license agreement. The complaint further alleges that the effect or tendency of the unfair methods of competition and unfair acts is to destroy or substantially injure an efficiently and economically operated domestic industry and/or to prevent the establishment of such an industry in the United States.

The complainant requests the Commission to institute an investigation and, after a full investigation, to issue a permanent exclusion order and permanent cease and desist orders.

FOR FURTHER INFORMATION CONTACT: Stephen L Sulzer, Esq., or Denise T. DiPersio, Esq., Unfair Import Investigations Division, U.S. International Trade Commission, telephone 202–523–0419 or 202–523–0113 respectively.

Authority

The authority for institution of this investigation is contained in section 337 of the Tariff Act of 1930 and in § 210.12 of the Commission's Rules of Practice and Procedure (19 CFR 210.12).

Scope of Investigation

Having considered the complaint, the U.S. International Trade Commission, on January 10, 1985, ordered that—

(1) Pursuant to subsection (b) of section 337 of the Tariff Act of 1930, an investigation be instituted to determine whether there is a violation of subsection (a) of section 337 in the unlawful importation of certain fluidized bed combustion systems into the United States, or in their sale, by reason of alleged: (1) infringement of claims 1, 4, 5, and 8 of U.S. Letters Patent 4,279,205; (2) infringement of claims 1, 2, 4, and 5 of U.S. Letters Patent 4,303,023; (3) misappropriation of trade secrets; and (4) fraudulent inducement to enter into a license agreement, the effect or tendency of which is to destroy or substantially injure an efficiently and economically operated domestic industry and/or to prevent the establishment of such an industry in the United States.

(2) For the purpose of the investigation so instituted, the following are hereby named as parties upon which this notice of investigation shall be served:

(a) The complainant is—Wormser Engineering, Inc., 225 Merrimac Street, P.O. Box 4007, Woburn, Massachusetts 01888.

(b) The respondents are the following companies, alleged to be in violation of section 337, and are the parties upon which the complaint is to be served:

ASEA STAL AB 5–61220, Finspong, Sweden

ASEA STAL. Inc., 50 Chestnut Ridge Road, Montvale, New Jersey 07645.

(c) Stephen L. Sulzer, Esq., and Denise T. DiPersio. Esq., Unfair Import Investigations Division, U.S. International Trade Commission, 701 E Street NW., Room 124, Washington, D.C. 20436, shall be the Commission investigative attorneys, party to this investigation; and

(3) For the investigation so instituted, Janet D. Saxon, Chief Administrative Law Judge, U.S. International Trade Commission, shall designate the presiding administrative law judge.

Responses must be submitted by the named respondents in accordance with § 210.21 of the Commission's Rules of Practice and Procedure (19 CFR 210.21 as amended, 49 FR 46123). Pursuant to §§ 201.16(d) and 210.21(a) of the rules, such responses will be considered by the Commission if received not later than 20 days after the date of service of the complaint. Extensions of time for submitting a response will not be granted unless good cause therefor is shown.

Failure of a respondent to file a timely response to each allegation in the complaint and in this notice may be deemed to constitute a waiver of the right to appear and contest the allegations of the complaint and this notice, and to authorize the Administrative Law Judge and the Commission, without further notice to the respondent, to find the facts to be as alleged in the complaint and this notice and to enter both an initial determination and a final determination containing such findings.

The complaint, except for any confidential information contained therein, is available for inspection during official business hours (8:45 a.m. to 5:15 p.m.) in the Office of the Secretary, U.S. International Trade Commission, 701 E Street NW., Room 156, Washington, D.C. 20436, telephone 202–523–0471.

Issued by: January 11, 1985.

By order of the Commission.

Kenneth R. Mason,

Secretary.

[FR Doc. 85–1652 Filed 1–22–85; 8:45 am]

BILLING CODE 7020–02–M

[Investigation No. 337–TA–201]

Certain Products with "Gremlins" Character Depiction; Commission Decision Not To Review Initial Determination

AGENCY: U.S. International Trade Commission.

ACTION: Nonreview of initial determination denying complainant's motion for temporary relief.

SUMMARY: The Commission has determined not to review the administrative law judge's initial determination (ID) in the above-captioned investigation denying the complaint's motion for a temporary exclusion order. The Commission adopted that portion of the administrative law judge's ID finding that there is no immediate and substantial harm to the domestic industry. The Commission took no position on the other issues discussed in the ID.

FOR FURTHER INFORMATION CONTACT: William Perry, Esq., Office of the General Counsel, U.S. International Trade Commission, telephone 202–523–0499.

SUPPLEMENTARY INFORMATION: On July 25, 1984, complainant Warner Bros., Inc., filed a complaint under section 337 and a motion for expedited temporary relief. On August 22, 1984 the Commission instituted an investigation under section 337 to determine whether there are unfair methods of competition and unfair acts in the importation of certain "Gremlins" character depictions into the United States, or in their sale, by reason of alleged infringement of (1) U.S. Copyright Reg. No. VAu 54–951; (2) U.S. Copyright Reg. No. VAu 54–952; and (3) U.S. Copyright Reg. No. PAu 214–201, the effect or tendency of which is to destroy or substantially injure an industry, effeciently and economically operated, in the United States. The notice of investigation named 31 respondents.

On December 10, 1984, The administrative law judge issued an ID denying complainant's motion for temporary relief. The Commission received no petitions for review of the ID from any party to the investigation or comments from any Government agency.

The authority for the Commission's action is contained in section 337 of the Tariff Act of 1930 and in § 210.53 of the Commission's Rules of Practice and Procedure (49 FR 46137 (November 23, 1984), to be codified at (19 CFR 210.53)).

Notice of this investigation was published in the **Federal Register** August 30, 1984 (49 FR 34422–23).

Copies of the public version of the ID and all other nonconfidential documents filed in connection with this investigation are available for inspection during official business hours 8:45 a.m. to 5:15 p.m.) in the Office of the Secretary, U.S. International Trade Commission, 701 E Street NW., Washington, D.C. 20436, telephone 202–523–0161.

Issued: January 4, 1985.

By order of the Commission

Kenneth R. Mason,

Secretary.

[FR Doc. 85–1648 Filed 1–22–85; 8:45 am]

BILLING CODE 7020–02–M

[Investigation No. 731–TA–238 (Preliminary)]

12-Volt Motorcycle Batteries From Taiwan

AGENCY: United States International Trade Commission.

ACTION: Institution of a preliminary antidumping investigation and scheduling of a conference to be held in connection with the investigation.

SUMMARY: The Commission hereby gives notice of the institution of preliminary antidumping investigation No. 731–TA–238 (Preliminary) under section 733(a) of the Tariff Act of 1930 (19 U.S.C. 1673(a)) to determine whether there is a reasonable indication that an industry in the United States is materially injured, or is threatened with material injury, or the establishment of an industry in the United States is materially retarded, by reason of imports from Taiwan of 12-volt lead-acid type motorcycle batteries, provided for in item 683.05 of the Tariff Schedules of the United States, which are alleged to be sold in the United States at less than fair value. As provided in section 733(a), the Commission must complete preliminary antidumping investigations in 45 days, or in this case by February 25, 1985.

For further information concerning the conduct of this investigation and rules of general application, consult the Commission's Rules of Practice and Procedure, Part 207, Subparts A and B (19 CFR Part 207), and Part 201, Subparts A through E (19 CFR Part 201).

EFFECTIVE DATE: January 11, 1985.

FOR FURTHER INFORMATION CONTACT: Bruce Cates (202–523–0369), Office of Investigations, U.S. International Trade Commission, 701 E Street NW., Washington, DC 20436.

SUPPLEMENTARY INFORMATION:

Background

This investigation is being instituted in response to a petition filed on January 11, 1985, by General Battery Corp., Reading, PA.

Participation in the Investigation

Persons wishing to participate in this investigation as parties must file an entry of appearance with the Secretary to the Commission, as provided in § 201.11 of the Commission's rules (19 CFR 201.11), not later than seven (7) days after publication of this notice in the **Federal Register**. Any entry of appearance filed after this date will be referred to the Chairwoman, who will determine whether to accept the late entry for good cause shown by the person desiring to file the entry.

Service List

Pursuant to § 201.11(d) of the Commission's rules (19 CFR 201.11(d)), the Secretary will prepare a service list containing the names and addresses of all persons, or their representatives, who are parties to this investigation upon the expiration of the period for filing entries of appearance. In accordance with § 201.16(c) of the rules (19 CFR 201.16(c)), each document filed by a party to the investigation must be served on all other parties to the investigation (as identified by the service list), and a certificate of service must accompany the document. The Secretary will not accept a document for filing without a certificate of service.

Conference

The Director of Operations of the Commission has scheduled a conference in connection with this investigation for 9:30 a.m. on February 1, 1985, at the U.S. International Trade Commission Building, 701 E Street NW., Washington, DC. Parties wishing to participate in the conference should contact Bruce Cates (202–523–0369) not later than January 31, 1985, to arrange for their appearance. Parties in support of the imposition of antidumping duties in this investigation and parties in opposition to the imposition of such duties will each be collectively allocated one hour within which to make an oral presentation at the conference.

Written Submissions

Any person may submit to the Commission on or before February 6, 1985, a written statement of information pertinent to the subject of the investigation, as provided in § 207.15 of the Commission's rules (19 CFR 207.15). A signed original and fourteen (14) copies of each submission must be filed with the Secretary to the Commission in accordance with § 201.8 of the rules (19 CFR 201.8). All written submissions except for confidential business data will be available for public inspection during regular business hours (8:45 a.m. to 5:15 p.m.) in the Office of the Secretary to the Commission.

Any business information for which confidential treatment is desired must be submitted separately. The envelope and all pages of such submissions must be clearly labeled "Confidential

Business Information." Confidential submissions and requests for confidential treatment must conform with the requirements of § 201.6 of the Commission's rules (19 CFR 201.6, as amended by 49 FR 32569, August 15, 1984).

Authority

This investigation is being conducted under authority of the Tariff Act of 1930, title VII. This notice is published pursuant to § 207.12 of the Commission's rules (19 CFR 207.12).

Issued: January 15, 1985.

By order of the Commission.

Kenneth R. Mason,

Secretary.

[FR Doc. 85-1651 Filed 1-22-85; 8:45 am]

BILLING CODE 7020-02-M

[Investigation No. 337-TA-185]

Certain Rotary Wheel Printing Systems; Commission Decision Not To Review Initial Determination Terminating Respondents Primages, Inc. and Primages, Inc.-ROC; Issuance of Consent Order

AGENCY: U.S. International Trade Commission.

ACTION: Termination of respondents on the basis of a settlement agreement and a consent order.

SUMMARY: Termination of the investigation with respect to the Primages respondents furthers the public interest by conserving Commission resources and those of the parties involved.

FOR FURTHER INFORMATION CONTACT: George Holoch, Esq., Office of the General Counsel, U.S. International Trade Commission, telephone 202-523-0148.

SUPPLEMENTARY INFORMATION: This action is taken pursuant to the authority of 19 U.S.C. 1337 and 19 CFR 210.53.

The Commission has determined that the consent order will have no negative effects on the public health and welfare, competitive conditions in the U.S. economy, the production of like or directly competitive articles in the United States, or U.S. consumers.

Notice of the ID was published in the **Federal Register** of December 19, 1984, 49 FR 49392. No petition for review was filed, nor were any comments from Government agencies or the public received.

Copies of the ID and all other nonconfidential documents filed in connection with this investigation are available for inspection during official business hours (8:45 a.m. to 5:15 p.m.) in the Office of the Secretary, U.S. International Trade Commission, 701 E Street NW., Washington, D.C. 20436, telephone 202-523-061.

Issued: January 14, 1985.

By order of the Commission.

Kenneth R. Mason,

Secretary.

[FR Doc. 85-1655 Filed 1-22-85; 8:45 am]

BILLING CODE 7020-02-M

[Investigation No. 337-TA-174]

Certain Woodworking Machines; Receipt of Initial Determination Terminating Respondents on the Basis of Consent Order Agreement

AGENCY: U.S. International Trade Commission.

ACTION: Notice is hereby given that the Commission has received an initial determination from the presiding officer in the above-captioned investigation terminating the following respondents on the basis of a consent order agreement: Nu-Way Machinery Corporation; Tien Chien Enterprises Co., Ltd.; Equipment Importers, Inc.; Yung Li Hsing Electric Works Co., Ltd.; Chiu Ting Machinery Co. Ltd.; Upsix Industrial Co., Ltd.; Grizzly Imports, Inc.; Shih Hsin Machinery Industrial Co., Ltd., Dankey International Incorporated; Kuang Yung Machinery Co., Ltd.; Astro-Pneumatic Tool Co.; Shen Kung Machinery Industrial Co., Ltd.; Taiwan Sheng Tsai Industrial Co., Ltd.

SUPPLEMENTARY INFORMATION: This investigation is being conducted pursuant to section 337 of the Tariff Act of 1930 (19 U.S.C. 1337). Under the Commission's rules, the presiding officer's initial determination will become the determination of the Commission thirty (30) days after the date of its service upon the parties, unless the Commission orders review of the initial determination. The initial determination in this matter was served upon the parties on January 14, 1985.

Copies of the initial determination, the consent order agreement, and all other nonconfidential documents filed in connection with this investigation are available for inspection during official business hours (8:45 a.m. to 5:15 p.m.) in the Office of the Secretary, U.S. International Trade Commission, 701 E Street NW., Washington, D.C. 20436, telephone 202-523-0161.

Written Comments

Interested persons may file written comments with the Commission concerning termination of the aforementioned respondents. The original and 14 copies of all such comments must be filed with the Secretary to the Commission, 701 E Street, NW., Washington, D.C. 20436, no later than 10 days after publication of this notice in the **Federal Register**. Any person desiring to submit a document (or portion thereof) to the Commission in confidence must request confidential treatment. Such requests should be directed to the Secretary to the Commission and must include a full statement of the reasons why confidential treatment should be granted. The Commission will either accept the submission in confidence or return it.

FOR FURTHER INFORMATION CONTACT: Ruby J. Dionne, Office of the Secretary, U.S. International Trade Commission, telephone 202-523-0176.

Issued: January 14, 1985.

By order of the Commission.

[FR Doc. 85-1647 Filed 1-22-85; 8:45 am]

BILLING CODE 7020-02-M

INTERSTATE COMMERCE COMMISSION

Forms Under Review by Office of Management and Budget

The following proposal for collection of information under the provisions of the Paperwork Reduction Act (44 U.S.C. Chapter 35) is being submitted to the Office of Management and Budget for review and approval. Copies of the forms and supporting documents may be obtained from the Agency Clearance Officer, Ray Houser (202) 275-6723. Comments regarding this information collection should be addressed to Ray Houser, Interstate Commerce Commission, Room 1325, 12th and Constitution Ave., NW., Washington, DC 20423 and to Gary Waxman, Office of Management and Budget, Room 3228 NEOB, Washington, DC 20503, (202) 395-7340.

Type of Clearance: Revision and Extension

Bureau/Office: Bureau of Accounts

Title of Form: Annual Report of Railroad Employees, Service and Compensation; Quarterly Report of Railroad Employees, Service and Compensation; Monthly Report of Number of Employees Class I Railroads

OMB Form No.: 3120-0074

Agency Form No.: Annual wage A & B M-300 and monthly wage report of employees

Frequency: Monthly, Quarterly and Annually

Respondents: Class I Railroads

No. of Respondents: 27
Total Burden Hrs.: 18,819
Type of Clearance: Revision
Bureau/Office: Small Business Assistance Office
Title of Form: Profile of Minority—Female Owned Motor Carrier
OMB Form No.: 3120-0050
Agency Form No.: OPA-81-1 and OPA-81-2
Frequency: Annually—Biennially
Respondents: Minority—Female Owners of Motor Carriers
No. of Respondents: 36
Total Burden Hrs.: 9

James H. Bayne,

Secretary.

[FR Doc. 85-1690 Filed 1-22-85; 8:45 am]

BILLING CODE 7035-01-M

[Finance Docket No. 30602]

The Chesapeake and Ohio Railway Co.; Merger Exemption; The Covington and Cincinnati Elevated Railroad and Transfer and Bridge Co.; Exemption

The Chesapeake and Ohio Railway Company (C&O) and The Covington and Cincinnati Elevated Railroad and Transfer and Bridge Company (C&C) filed a notice of exemption for C&C to merge into C&O.

C&C is a wholly-owned subsidiary of C&O, operated by C&O. Consummation of the merger should promote corporate simplification and eliminate the expense and burden associated with maintenance of C&C as a separate corporate entity. Under the merger plan, C&C's separate corporate existence will be extinguished. All of C&C's assets and liabilities will be taken and vested in C&O. No reduction of transportation facilities are contemplated and no obligations of C&C will be impaired.

This is a transaction within a corporate family of the type specifically exempted from the necessity of prior review and approval under 49 U.S.C. 1180.2(d)(3). It will not result in adverse changes in service levels, significant operational changes, or a change in the competitive balance with carriers outside the corporate family.

As a condition to use of this exemption, any employees affected by the merger shall be protected pursuant to *New York Dock Ry.—Control—Brooklyn Eastern District,* 360 I.C.C. 60 (1979).

This notice is effective upon publication.

Decided: January 10, 1985.

By the Commission, Heber P. Hardy, Director, Office of Proceedings.

James H. Bayne,

Secretary.

[FR doc. 85-1689 Filed 1-22-85; 8:45 am]

BILLING CODE 7035-01-M

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

Manufacturer of Controlled Substances; Abbott Laboratories; Application

Pursuant to § 1301.43(a) of Title 21 of the Code of Federal Regulations (CFR), this is notice that on June 29, 1984, Abbott Laboratories, 14th and Sheridan Road, Attention: Customer Service D-345, North Chicago, Illinois 60064, made application to the Drug Enforcement Administration (DEA) for registration as a bulk manufacturer of the Schedule II controlled substance Pentobarbital (2270).

Any other such applicant and any person who is presently registered with DEA to manufacture such substance may file comments or objections to the issuance of the above application and may also file a written request for a hearing thereon in accordance with 21 CFR 1301.54 and in the form prescribed by 21 CFR 1316.47.

Any such comments, objections or requests for a hearing may be addressed to the Deputy Assistant Administrator, Drug Enforcement Administration, United States Department of Justice, 1405 I Street, NW., Washington, D.C. 20537, Attention: DEA Federal Register Representative (Room 1112), and must be filed no later than February 22, 1985.

Dated: January 15, 1985.

Gene R. Haislip,

Deputy Assistant Administrator, Office of Diversion Control, Drug Enforcement Administration.

[FR Doc. 85-1712 Filed 1-22-85; 8:45 am]

BILLING CODE 4410-09-M

Manufacturer of Controlled Substances; Arenol Chemical Corp.; Registration

By Notice dated September 5, 1984, and published in the **Federal Register** on September 12, 1984 (49 FR 35877), Arenol Chemical Corporation, 40-33 23rd Street, Long Island City, New York 11101, made application to the Drug Enforcement Administration to be registered as a bulk manufacturer of the basic classes of controlled substances listed below:

Drug	Schedule
Amphetamine (1100)	II
Methamphetamine (1105)	II

No comments or objections have been received. Therefore pursuant to Section 303 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 and Title 21, Code of Federal Regulations, § 1301.54(e), the Deputy Assistant Administrator hereby orders that the application submitted by the above firm for registration as a bulk manufacturer of the basic classes of controlled substances listed above is granted.

Dated January 15, 1985.

Gene R. Haislip,

Deputy Assistant Administrator, Office of Diversion Control, Drug Enforcement Administration.

[FR Doc. 85-1714 Filed 1-22-85; 8:45 am]

BILLING CODE 4410-09-M

Manufacturer of Controlled Substances; Ganes Chemicals, Inc.; Application

Pursuant to § 1301.43(a) of Title 21 of the Code of Federal Regulations (CFR), this is notice that on July 17, 1984, Ganes Chemicals, Inc. (lessee of Siegfried Chemicals, Inc.), Industrial Park Road, Pennsville, New Jersey 08070, applied to DEA to have the basic class of controlled substances listed below added to their registration as a bulk manufacturer:

Methadone (9250)	II
Methadone Intermediate: 4-cyano-2-dimethylamino-4,4-diphenyl butane (9254).	II

Any other such applicant, and any person who is presently registered with DEA to manufacture such substances, may file comments or objections to the issuance of the above application and may also file a written request for a hearing thereon in accordance with 21 CFR 1301.54 and in the form prescribed by 21 CFR 1316.47.

Any such comments, objections or requests for a hearing may be addressed to the Deputy Assistant Administrator, Drug Enforcement Administration, United States Department of Justice, 1405 I Street, NW., Washington, D.C. 20537, Attention: DEA Federal Register Representative (Room 1112), and must be filed no later than February 22, 1985.

Dated: January 16, 1985.

Gene R. Haislip,

Deputy Assistant Administrator, Office of Diversion Control, Drug Enforcement Administration.

[FR Doc. 85-1713 Filed 1-22-85; 8:45 am]

BILLING CODE 4410-09-M

Manufacturer of Controlled Substances; Marion Laboratories Inc., et al; Registration

By Notice dated October 24, 1984, and published in the **Federal Register** on November 1, 1984, (49 FR 44031), Marion Laboratories Inc., Analytical Systems, Inc. Division, 23162 La Cadena Drive, Laguna Hills, California 92653, made applicaton to the Drug Enforcement Administration to be registered as a bulk manufacturer of the basic classes of controlled substances listed below:

Drug	Schedule
1-Phenylcyclohexylamine (7460)	II
Ecgonine (9180)	II
Phencyclidine (7471)	II

No comments or objections have been received. Therefore pursuant to Section 303 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 and Title 21, Code of Federal Regulations § 1301.54(e), the Deputy Assistant Administrator hereby orders that the application submitted by the above firm for registration as a bulk manufacturer of the basic classes of controlled substances listed above is granted.

Dated: January 15, 1985.

Gene R. Haislip,

Deputy Assistant Administrator, Office of Diversion Control, Drug Enforcement Administration.

[FR Doc. 85-1711 Filed 1-22-85; 8:45 am]

BILLING CODE 4410-09-M

Manufacturer of Controlled Substances; Wyeth Laboratories Inc., Registration

By Notice dated August 27, 1984, and published in the **Federal Register** on September 5, 1984, (49 FR 35050), Wyeth Laboratories Inc., 611 East Nield Street, West Chester, Pennsylvania 19380, made applicaton to the Drug Enforcement Administration to be registered as a bulk manufacturer of the basic classes of controlled substances listed below:

Drug	Schedule
Patnoine (meperidine) (9230)	II
Pethidine-Intermediate (9232)	II

No comments or objections have been received. Therefore pursuant to Section 303 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 and Title 21, Code of Federal Regulations § 1301.54(e), the Deputy Assistant Administrator hereby orders that the application submitted by the above firm for registration as a bulk manufacturer of the basic classes of controlled substances listed above is granted.

Dated: January 15, 1985.

Gene R. Haislip,

Deputy Assistant Administrator, Office of Diversion Control, Drug Enforcement Administration.

[FR Doc. 85-1715 Filed 1-22-85; 8:45 am]

BILLING CODE 4410-09-M

DEPARTMENT OF LABOR

Pension and Welfare Benefit Programs

[Prohibited Transaction Exemption 85-13; Exemption Application No. D-2935 et al.]

Grant of Individual Exemptions; Citizens Banking of Evans City, et al.

AGENCY: Pension and Welfare Benefit Programs, Labor.

ACTION: Grant of individual Exemptions.

SUMMARY: This document contains exemptions issued by the Department of Labor (the Department) from certain of the prohibited transaction restrictions of the Employee Retirement Income Security Act of 1974 (the Act) and/or the Internal Revenue Code of 1954 (the Code).

Notices were published in the **Federal Register** of the pendency before the Department of proposals to grant such exemptions. The notices set forth a summary of facts and representations contained in each application for exemption and referred interested persons to the respective applications for a complete statement of the facts and representations. The applications have been available for public inspection at the Department in Washington, D.C. The notices also invited interested persons to submit comments on the requested exemptions to the Department. In additon the notices stated that any interested person might submit a written request that a public hearing be held (where appropriate). The applications have represented that they have complied with the requirements of the notification to interested persons. No public comments and no requests for a hearing, unless otherwise stated, where received by the Department.

The notices of pendency were issued and the exemptions are being granted solely by the Department because, effective December 31, 1978, section 102 of Reorganization Plan No. 4 of 1978 (43 FR 47713, October 17, 1978) transferred the authority of the Secretary of the Treasury to issue exemptions of the type proposed to the Secretary of Labor.

Statutory Findings

In accordance with section 408(a) of the Act and/or section 4975(c)(2) of the Code and the procedures set forth in ERISA Procedure 75-1 (40 FR 18471, April 28, 1975), and based upon the entire record, the Department makes the following findings:

(a) The exemptions are administratively feasible;

(b) They are in the interests of the plans and their participants and beneficiaries; and

(c) They are protective of the rights of the participants and beneficiaries of the plans.

Citizens Bank of Evans City Pension Plan and Trust (the Plan) Located in Evans City, Pennsylvania

[Prohibited Transaction Exemption 85-13; Exemption Application No. D-2935]

Exemption

The restrictions of section 406(a), 406(b)(1) and 406(b)(2) of the Act and the sanctions resulting from the application of section 4975 of the Code, by reason of section 4975(c)(1) (A) through (E) of the Code, shall not apply to: (1) The past lease (the Lease) of certain real property (the Property) by the Plan to the Citizens National Bank of Evans City, Pennsylvania (the Employer), the sponsor of the Plan; (2) the sale of the Property by the Plan to the Employer; and (3) the assumption by the Employer of certain indebtedness of the Plan; provided the terms and conditions of the Lease, the sale of the Property and the assumption of indebtedness by the Employer was and will be at least as favorable to the Plan as the Plan could obtain in an arm's length transaction between unrelated parties. The Lease was entered into before the effective date of the Act, but after July 1, 1974, the date specified in the transition rules contained in sections 414 and 2003 of the Act.

Effective Dates: The effective dates of this exemption, are Janaury 1, 1975 for the Lease; and the date the grant of the exemption is published in the **Federal Register** for the sale of the Property by the Plan to the Employer and the assumption by the Employer of the indebtedness of the Plan.

For a more complete statement of the facts and representations supporting the Department's decision to grant this exemption refer to the notice of proposed exemption published on November 16, 1984 at 49 FR 45504.

For Further Information Contact: Mr. Louis Campagna of the Department, telephone (202) 523–8971. (This is not a toll-free number.)

Southmark Realty Advisers, Inc. (Southmark) Located in Dallas, Texas

[Prohibited Transaction Exemption 85–14; Exemption Application No. D–3450]

Exemption

Section I—Exemption for Certain Transactions Involving the Purchase and Sale of Units of the Funds

The restrictions of section 406(a)(1)(A) through (D) of the Act and section 4975(c)(1)(A) through (D) of the Code shall not apply to the purchase and sale of units of the Funds between Southmark and an employee benefit plan that is participating in the Fund (Participating Plan) where Southmark provides or will provide investment management services and therefore is or will be a fiduciary, provided that:

(a) Each purchase and sale is authorized in writing by a fiduciary of a Participating Plan who is independent of Southmark and any of its affiliates;

(b) Not more than 5 percent of a Participating Plan's assets are invested in the Fund; and

(c) The applicable conditions set forth in Section V of this exemption are met.

Section II—Exemption for Certain Transactions Involving Collective Investment Funds Sponsored by Southmark

(a) *General Exemption.* The restrictions of sections 406(a), 406(b)(2) and 407(a) of the Act and the sanctions resulting from the application of section 4975 of the Code, by reason of section 4975(c)(1)(A) through (D) of the Code, shall not apply to the transactions described below if the applicable conditions set forth in Section V are met.

(1) *Transactions Between Parties in Interest and the Funds.* Any transaction between a party in interest with respect to a Participating Plan and the Fund, or any acquisition, sale, leasing or holding by the Fund of employer securities or employer real property, if at the time of the transaction, acquisition, sale, lease or holding—

(A) The party in interest is not Southmark or one of its affiliates, and

(B) The interest of the Participating Plan together with the interests of any other plans maintained by the same employer or employee organization in the Fund does not exceed 10 percent of the total of all assets in the Fund.

(2) *Acquisitions, Sales, Leasing or Holding of Employer Securities and Employer Real Property.* (A) Except as provided in subparagraph (B) of this paragraph, any acquisition, sale, leasing or holding of employer securities or employer real property by the Fund which does not meet the requirements of paragraph (a)(1) of this Section II, if no commission is paid to Southmark or to any affiliate of Southmark or the employer in connection with the acquisition or sale of employer securities or the acquisition, sale or lease of employer real property, and

(i) In the case of employer real property—

(aa) Each parcel of employer real property and the improvements thereon held by the Fund are suitable (or adaptable without excessive cost) for use by different tenants, and

(bb) The employer real property of the Fund that is leased or held for lease to others, in the aggregate, is dispersed geographically.

(ii) In the case of employer securities—

(aa) Neither Southmark nor any of its affiliates is the issuer of the security, and

(bb) If the security is an obligation of the issuer, either

(1) The Fund owns the obligation at the time the Participating Plan acquires an interest in the Fund, and interests in the Fund are offered and redeemed in accordance with valuation procedures of the Fund applied on a uniform or consistent basis, or

(2) Immediately after acquisition of the obligation by the Fund: (AA) Not more than 25 percent of the aggregate amount of obligations issued in the issue and outstanding at the time of acquisition is held by a Participating Plan, and (BB) at least 50 percent of the aggregate amount of obligations issued in the issue and outstanding at the time of acquisition is held by persons independent of the issuer. Southmark, its affiliates and any Fund maintained by Southmark or its affiliates shall be considered to be persons independent of the issuer if Southmark is not an affiliate of the issuer.

(B) In the case of a Participating Plan that is not an eligible individual account plan (as defined in section 407(d)(3) of the Act), the exemption provided in subparagraph (A) of this paragraph shall be available only if, immediately after the acquisition of the securities or real property, the aggregate fair market value of employer securities and employer real property with respect to which Southmark or its affiliate has investment discretion does not exceed 10 percent of the fair market value of all the assets of the Participating Plan with respect to which Southmark or its affiliate has investment discretion.

(C) For the purposes of the exemption contained in subparagraph (A) of this paragraph, the term "employer securities" shall include securities issued by, and the term "employer real property" shall include real property leased to, a person who is a party in interest with respect to a Participating Plan by reason of a relationship to the employer described in section 3(14) (E), (G), (H) or (I) of the Act.

(b) *Special Exemptions.* The restrictions of section 406(a) and section 406(b) (1) and (2) of the Act and the sanctions resulting from the application of section 4975 of the Code by reason of section 4975(c)(1) (A) through (E) shall not apply to the transactions described below, if the conditions of Section V are met.

(1) *Certain Leases and Goods.* The furnishing of goods to the Fund by a party in interest with respect to a Participating Plan or the leasing of real property owned by the Fund to such party in interest and the incidental furnishing of goods to such party in interest by the Fund, if—

(A) In the case of goods, they are furnished to or by the Fund in connection with real property owned by the Fund,

(B) The party in interest is not Southmark, any affiliate of Southmark, or another Fund, and

(C) The amount involved in the furnishing of goods or leasing of real property in any calendar year (including the amount under any other lease or arrangement for the furnishing of goods in connection with the real property investments of the Fund with the same party in interest, or any affiliate thereof) does not exceed the greater of $25,000 or 0.5 percent of the fair market value of the assets of the Fund on the most recent valuation date of the Fund prior to the transaction.

(2) *Management of Real Property.* Any services provided to the Fund by Southmark or by an affiliate of Southmark in connection with the management of the real property owned by the Fund, if:

(A) The compensation paid to Southmark or its affiliate does not exceed the compensation charged by qualified, unaffiliated persons for performing similar services in the area in which the Fund property is located; and

(B) The provisions of such services and the fees paid are negotiated, approved and monitored by a majority of the independent Fund trustees (the Independent Trustees).

(3) *Transactions Involving Places of Public Accommodation.* The furnishing of services, facilities and any goods incidental to such services and facilities by a place of public accommodation owned by the Fund to a party in interest with respect to a Participating Plan, if the services, facilities and incidental goods are furnished on a comparable basis to the general public.

(c) *Brokerage Fees.* The restrictions of section 406 of the Act and the sanctions resulting from the aplication of section 4975 of the Code by reason of section 4975(c)(1) (A) through (F) shall not apply to any services provided to the Fund by Southmark or by an affiliate of Southmark in connection with the acquisition or sale by the Fund of real property, if:

(1) The commission paid to Southmark or its affiliate either by the Fund or a third party seller does not exceed the commission that would be paid to an unrelated third party in an arm's-length transaction; and

(2) The provision of such services and the commissions paid by the Fund are negotiated, approved and monitored by a majority of the Independent Trustees.

Section III—Excess Holding Exemption for Participating Plans

The restrictions of sections 406(a) and 407(a) of the Act and the sanctions resulting from the application of section 4975 of the Code by reason of section 4975(c)(1) (A) through (D) of the Code shall not apply to any acquisition or holding of qualifying employer securities or qualifying employer real property (other than through the Fund) by a Participating Plan If—

(a) The acquisition or holding contravenes the restrictions of sections 406(a)(1)(E), 406(a)(2) and 407(a) of the Act solely by reason of being aggregated with employer securities or employer real property held by the Fund,

(b) The requirements of either paragraph (a)(1) or (2) of Section II of this exemption are met, and

(c) The applicable conditions set forth in Section V of this exemption are met.

Section IV—Transactions With Persons Who Are Parties In Interest With Respect to a Participating Plan Solely by Virtue of Being Certain Service Providers or Certain Affiliates of Service Providers

The restrictions of section 406(a) of the Act and the taxes imposed by section 4975 (a) and (b) of the Code by reason of section 4975(c)(1) (A) through (D) of the Code shall not apply to any transaction between the Fund and a person who is a party in interest with respect to a Participating Plan that has an interest in the Fund, if—

(a) The person is a party in interest (including a fiduciary) solely by reason of providing services to the Participating Plan, or solely by reason of a relationship to a service provider described in section 3(14) (F), (G), (H) or (I) of the Act, or both, and the person neither exercised nor has any discretionary authority, control, responsibility or influence with respect to the investment of the Participating Plan's assets in, or held by, the Fund;

(b) The person is not Southmark or any affiliate thereof; and

(c) The person is a party in interest with respect to a Participating Plan, which Participating Plan's interest in the Fund, together with the interest(s) held by any other plans maintained by the same employer or employee organization, does not exceed 20 percent of the total assets of the Fund.

Section V—General Conditions

(a) At the time the transaction is entered into, and at the time of any subsequent renewal thereof that requires that consent of Southmark or its affiliate, the terms of the transaction are less favorable to the Fund than the terms generally available in arm's-length transactions between unrelated parties.

(b) Southmark or its affiliate maintains for a period of six years from the date of the transaction the records necessary to enable the persons described in subsection (c) of this section to determine whether the conditions of this exemption have been met, except that (1) a prohibited transaction will not be considered to have occurred if, due to circumstances beyond the control of Southmark or its affiliate, the records are lost or destroyed prior to the end of the six-year period, and (2) no party in interest shall be subject to the civil penalty that may be assessed under section 502(i) of the Act, or to the taxes imposed by section 4975 (a) and (b) of the Code, if the records are not maintained, or are not available for examination as required by subsection (c) below.

(c)(1) Except as provided in paragraph (2) below and notwithstanding any provisions of subsections (a)(2) and (b) of section 503 of the Act, the records referred to in subsection (b) of this section are unconditionally available at their customary location for examination during normal business hours by:

(A) Any duly authorized employee or representative of the Department of the Internal Revenue Service.

(B) Any fiduciary of a Participating Plan who has authority to acquire or dispose of the interests in the Fund or any duly authorized employee or representative of such fiduciary,

(C) Any contributing employer to any Participating Plan, or any duly authorized employee or representative of such employer, and

(D) Any participant or beneficiary of any Participating Plan, or any duly authorized employee or representative of such participant or beneficiary.

(2) None of the persons described in subparagraph (B) through (D) above shall be authorized to examine trade secrets of Southmark or its affiliates, or commercial or financial information which is privileged or confidential.

Section VI—Definitions and General Rules

For purposes of this exemption,

(a) An "affiliate" of a person includes—

(1) Any person directly or indirectly through one or more intermediaries, controlling, controlled by, or under common control with the person,

(2) Any officer, director, employee, relative of, or partners in any such person, and

(3) Any corporation or partnership of which such person is an officer, director, partner or employee.

For the purposes of this subsection (a), the term "affiliate" shall not be limited to persons or entities that are in existence of the effective date of this exemption.

(b) The term "control" means the power to exercise a controlling influence over the management or policies of a person other than an individual.

(c) The term "relative" means a "relative" as that term is defined in section 3(15) of the Act (or a "member of the family" as that term is defined in section 4975(e)(6) of the Code), or a brother, a sister, or a spouse of a brother or sister.

(d) The term "Fund" means any collective investment fund that is currently managed by Southmark or its affiliates and any collective investment fund that may hereafter be established and managed by Southmark or its affiliates, provided that in all material respects such Funds will be similar. The term "Funds" shall mean all of the collective investment funds.

(e) The time as of which any transaction, acquisition or holding occurs is the date upon which the transaction is entered into, the

acquisition is made or the holding commences. In addition, in the case of a transaction that is continuing, the transaction shall be deemed to occur until it is terminated. If any transaction is entered into, or any acquisition is made, on or after the date of granting of this exemption, or a renewal that requires the consent of the Fund occurs on or after the date of granting of this exemption, and the requirements of this exemption are satisified at the time the transaction is entered into or renewed, respectively, or at the time the acquisition is made, the requirements will continue to be satisfied thereafter with respect to the transaction or acquisition and the exemption shall apply thereafter to the continued holding of the property so acquired. Notwithstanding the foregoing, this exemption shall cease to apply to a transaction or holding exempt by virtue of Section II(a)(1) and IV at such time as the interest of any Participating Plan exceeds the percentage interest limiations of Section II(a)(1) and IV respectively, unless no portion of such excess results from the purchase of an additional interest in the Fund by such Participating Plan. For this purpose, purchases do not include the reinvestment of Fund earnings. Nothing in this subsection (e) shall be construed to exempt a transaction entered into by the Fund which becomes a transaction described in section 406 of the Act or section 4975 of the Code while the transaction is continuing, unless the conditions of the exemption were met either at the time the transaction was entered into or at the time the transaction would have become prohibited but for this exemption.

(f) Each Participating Plan shall be considered to own the same proportionate undivided interest in each asset of the Fund as its proportionate interest in the total assets of the Fund as calculated on the most recent preceding valuation date of the Fund.

(g) The term "Independent Trustee" means a party who: (1) Is not otherwise affilated with the Fund's investment manager, broker or property manager, (2) is not a fiduciary of any Participating Plan, (3) is not subject to the authority or control of the Fund's investment manager, broker or property manager or their affiliates, and (4) has acknowledged in writing his or her acceptance of the fiduciary obligations and agreed not to participate in any decision with respect to any transaction in which the Independent Trustee has an interest that might affect his or her best judgement.

For a more complete statement of the facts and representations supporting the Department's decision to grant this exemption refer to the notice of proposed exemption published on September 21, 1984 at 49 FR 37190.

Written Comments

The only comment received by the Department was submitted by the applicants who have requested that the language of representation number seven be modified. As included in the proposal, the representation stated that ". . . none of the individual Trustees nor any of the employees, officers, directors or shareholders of Southmark serve as fiduciaries of the Participating Plans, or as directors or officers of the sponsors of such plans." The applicant represents that as a practical matter it would be difficult if not impossible for Southmark to verify that no director, officer or any fiduciary of a plan sponsor to a Participating Plan has personally acquired stock in Southmark's parent, a publicly owned corporation. The Department has concluded that the participants and beneficiaries of Participating Plans would not be adversely affected should the representation be modified to limit its applicability to individuals exercising discretionary authority or otherwise participating in the decisions by such plans to invest in the Funds.

The Department would also note that the representation recited above is inadequate because it contained no reference to Southmark Corporation, the parent of Southmark Realty Advisors, or their affiliates. Therefore, in order to provide adequate protections for the participants and beneficiaries of the Participating Plans against potential conflict of interest decisions by the investing fiduciaries of such plans, the Department has determined that the representation should be expanded to include Southmark Corporation and its affiliates and any affiliates of Southmark Realty Advisors. Accordingly, the applicant has responded to the Department's concern by modifying the representation to read: ". . . none of the individual Trustees nor any of the employees, officers, directors or shareholders of Southmark, Southmark Corporation, or their affiliates will exercise any discretionary authority or otherwise participate in the decision of any Participating Plans to invest in the Fund." The Department acknowledges this change to the representations and incorporates such change in the grant.

For Further Information Contact: Paul R. Antsen of the Department, telephone (202) 523-6915. (This is not a toll-free number.)

A.B. Dick Products Company of Des Moines Employees Profit Sharing Plar and Trust (the Plan) Located in Des Moines, Iowa

[Prohibited Transaction Exemption 85-15; Exemption Application No. D-5234]

Exemption

The restrictions of section 406(a) and 406 (b)(1) and (b)(2) of the Act and the sanctions resulting from the application of section 4975 of the Code, by reason of section 4975(c)(1) (A) through (E) of the Code, shall not apply for a period of five years from the date of this grant to: (1) The purchase by the plan of certain leases of equipment (the Leases) from A.B. Dick Products Company of Des Moines (the Employer); and (2) the agreement by the Employer to indemnify the Plan against any loss relating to the Leases and also to repurchase any Leases that are in default in accordance with paragraph (C) below, provided the following conditions are met:

A. Any sale of Leases to the Plan will be on terms at least as favorable to the Plan as an arm's length transaction with an unrelated third party would be.

B. The acquisition of a Lease from the Employer shall not cause the Plan to hold immediately following the acquisition: (i) More than 50 percent of the current value (as that term is defined in section 3(26) of the Act) of Plan assets in Leases sold by the Employer; or (ii) more than 10 percent of Plan assets (as defined above) in Leases of any one lessee.

C. Upon default by the lessee on any payment due under a Lease, the Employer guarantees in writing the immediate payment of all remaining rental payments and all other amounts due and owing under the Lease. A Lease shall be deemed to be in default for purposes of this section, if a payment due under the terms and conditions of the Lease is past due for 30 days; or in the event the lessee shall become insolvent, commit an act of bankruptcy, make an assignment for the benefit of creditors or a liquidating agent, offer a composition or extension to creditors, make a bulk sale; or in the event any proceeding, suit or action at law, in equity or under any of the provisions of the Bankruptcy Act or of amendments thereto for reorganization, composition, extension, arrangements, receivership liquidation, or dissolution shall be begun by or against the lessee; or in the event of the appointment under any jurisdiction at law or in equity of any receiver of any property of the lessee; or

in the event the condition of affairs of the lessee shall so change as to, in the opinion of the Trustee or other appropriate Plan fiduciaries, impair its security or increase its credit risk.

D. The Plan receives adequate security for the property underlying the Lease. For purposes of this exemption, the term adequate security means that the property is secred by a perfected security interest in the property leased, so that, if there is a default on the Lease, and the security is foreclosed upon, or otherwise disposed of, the value and liquidity of the security is such that it may reasonably be anticipated that the Plan will experience no loss.

E. Insurance against loss or damage to the leased property from fire or other hazards will be procured and maintained by the lessee, and the proceeds from such insurance will be assigned to the Plan.

F. The Plan shall maintain for the duration of any Lease which is sold to the Plan pursuant to this exemption, records necessary to determine whether the conditions of this exemption have been met. The records above must be unconditionally available at their customary location for examination, for purposes reasonably related to protecting rights under the Plan, during normal business hours by the Internal Revenue Service, the Department of Labor, Plan participants, any employer of Plan participants, any employee organization any of whose members are covered by the Plan, or any duly authorized employee or representative of the above described persons.

For a more complete statement of the facts and representations supporting the Department's decision to grant this exemption refer to the notice of proposed exemption published on November 16, 1984 at 49 FR 45505.

For Further Information Contact: David M. Cohen of the Department, telephone (202) 523–8671. (This is not a toll-free number.)

McNichols Profit Sharing Plan (the Plan) Located in Cleveland, Ohio

[Prohibited Transaction Exemption 85–16; Exemption Application No. D–5382]

Exemption

The restrictions of section 406(a), 406(b)(1) and 406(b)(2) of the Act and the sanctions resulting from the application of section 4975 of the Code, by reason of section 4975(c)(1) (A) through (E) of the Code, shall not apply to: (1) The proposed loan (the Loan) by the Plan to Rockwall Properties of the lesser of $660,000 or 24% of the Plan's assets, provided that the terms and conditions of the Loan are not less favorable to the Plan than those obtainable in an arm's length transaction with an unrelated party on the date of the Consummation of the Loan; and (2) the guarantee of the Loan by McNichols Company, the employer whose employees are covered by the Plan.

For a more complete statement of the facts and representations supporting the Department's decision to grant this exemption refer to the notice of proposed exemption published on November 9, 1984 at 49 FR 44824.

For Further Information Contact: Mrs Mary Jo Fite of the Department, telephone (202) 523–8671. (This is not a toll-free number.)

Coldevin B. Carlson, M.D., P.S., Money Purchase Pension Plan (the Plan), Located in Seattle, Washington

[Prohibited Transaction Exemption 85–17; Exemption Application No. D–5416]

Exemption

The sanctions resulting from the application of section 4975 of the Code, by reason of section 4975(c)(1) (A) through (E) of the Code, shall not apply to the sale of certain artwork by the Plan to Dr. and Mrs. Coldevin B. Carlson, who are disqualified persons with respect to the Plan, provided the purchase price is not less than the fair market value of the artwork on the date of sale.

Since Dr. Coldevin B. Carlson is the sole shareholder of Coldevin B. Carlson, M.D., P.S., the Plan sponsor, and the only participant in the Plan, there is no jurisdiction under Title I of the Act pursuant to 29 CFR 2510.3–3(b). However, there is jurisdiction under Title II of the Act pursuant to section 4975 of the Code.

For a more complete statement of the facts and representations supporting the Department's decision to grant this exemption refer to the notice of proposed exemption published on November 23, 1984 at 49 FR 46215.

For Further Information Contract: Ms. Linda M. Hamilton of the Department, telephone (202) 523–8881. (This is not a toll-free number.)

Duriron Company, Inc. Pension Trust for Salaried Employees (the Plan) Located in Dayton, Ohio

[Prohibited Transaction Exemption 85–18 Exemption Application No. D–5423]

Exemption

The restrictions of sections 406(a), 406(b)(1) and 406(b)(2) of the Act and the sanctions resulting from the application of section 4975 of the Code, by reason of section 4975(c)(1) (A) through (E) of the Code, shall not apply to (1) the continued leasing by the Plan, beyond June 30, 1984, of certain real property to Duriron Company, Inc. (the Employer), the sponsor of the Plan and a party in interest with respect to the Plan; and (2) the possible sale of the Property by the Plan to the Employer pursuant to a right of first refusal or put option, provided that the terms and conditions of the transactions are no less favorable to the Plan than those which could be obtained by the Plan in similar transactions with an unrelated party.

For a more complete statement of the facts and representations supporting the Department's decision to grant this exemption, refer to the notice of proposed exemption published on November 23, 1984, at 49 FR 46216.

Effective Date: This exemption is effective July 1, 1984.

For Further Information Contact: Ms. Katherine D. Lewis of the Department, telephone (202) 523–8882. (This is not a toll-free number.)

Truman Arnold Retirement Trust (the Plan) Located in Texarkana, Texas

[Prohibited Transaction Exemption 85–19; Exemption Application No. D–5466]

Exemption

The restrictions of sections 406(a), 406(b)(1) and 406(b)(2) of the Act and the sanctions resulting from the application of section 4975 of the Code, by reason of section 4975(c)(1) (A) through (E) of the Code, shall not apply to the continued leasing beyond June 30, 1984, of certain real property by the Plan to Truman Arnold Distributing Co., Inc., a party in interest to the Plan, provided that the terms of the lease are at least as favorable to the Plan as those obtainable in an arm's length transaction with an unrelated party.

Effective Date: The exemption is effective July 1, 1984.

For a more complete statement of the facts and representations supporting the Department's decision to grant this exemption refer to the notice of proposed exemption published on November 16, 1984 at 49 FR 45508.

For Further Information Contact: Mrs. Mary Jo Fite of the Department, telephone (202) 523–8671. (This is not a toll-free number.)

Stamford Computer Group, Inc. Defined Benefit Pension Trust (the Plan) Located in Stamford, Connecticut

[Prohibited Transaction Exemption 85–20; Exemption Application No. D–5599]

Exemption

The sanctions resulting from the application of section 4975 of the Code, by reason of section 4975(c)(1) (A) through (E) of the Code, shall not apply for a period of five years from the date of this grant to: (1) The purchase by the Plan of certain leases of computer equipment (the Leases) from Stamford Computer Group, Inc. (the Employer); and (2) the agreement by the Employer to indemnify the Plan against any loss relating to the Leases that are in default in accordance with paragraph (C) below, provided that the following conditions are met:

A. Any sale of Leases to the Plan will be on terms at least as favorable to the Plan as an arm's length transaction with an unrelated third party would be.

B. The acquisition of a Lease from the Employer shall not, immediately followng the acquisition, cause the Plan to hold more than 25 percent of the current value (as that term is defined in section 3(26) of the Act) of Plan assets in Leases sold by the Employer;

C. Upon default by the lessee on any payment due under a Lease, the Employer gurantees in writing the immediate payment of all remaining rental payments and all other amounts due and owing under the Lease. A Lease shall be deemed to be in default for purposes of this section, if a payment due under the terms and conditions of the Lease is past due for 10 days; or in the event the lessee shall become insolvent, commit an act of bankruptcy, make an assignment for the benefit of creditors or a liquidating agent, offer a composition or extension to creditors, make a bulk sale; or in the event any proceedings, suit or action at law, in equity or under any of the provisions of the Bankruptcy Act or of amendments thereto for reorganization, composition, extension, arrangements, receivership, liquidation, or dissolution shall be begun by or against the lessee; or in the event of appointment under any jurisdiction at law or in equity of any receiver or any property of the lessee; or in the event the condition of affairs of the lessee shalll so change as to, in the opinion of the independent fiduciary (discussed below), impair its security or increase its credit risk.

D. The Plan receives adequate security for the property underlying the Lease. For purposes of this exemption, the term adequate security means that the property is secured by a perfected security interest in the property leased, so that if there is a default on the Lease and the security is foreclosed upon or otherwise disposed of, the value and liquidity of the security is such that is may reasonably be anticipated that the Plan will experience no loss.

E. Insurance against loss or damage to the leased property from fire or other hazards will be procured and maintained by the lessee, and the proceeds from such insurance will be assigned to the Plan.

Temporary Nature of the Exemption: This exemption, if granted, will be temporary in nature and will expire 5 years after the date of grant with respect to the acquisition of Leases from the Employer.

For a more complete statement of the facts and representations supporting the Department's decision to grant this exemption refer to the notice of proposed exemption published on December 4, 1984 at 49 FR 47454.

For Further Information Contact: Mr. David M. Cohen of the Department, telephone (202) 523–8671. (This is not a toll-free number.)

Bass Investment Limited Partnership (the Partnership) Located in Fort Worth, Texas

[Prohibited Transaction Exemption 85–21; Exemption Application No. D–5634]

Exemption

The restrictions of section 406(a) of the Act and the sanctions resulting from the application of section 4975 of the Code, by reason of section 4975(c)(1) (A) through (D) of the Code, shall not apply, effective July 9, 1984, to the purchase or sale of securities between the Partnership and employee benefit plans (the Plans) with respect to which the Partnership is a party in interest, provided that the terms of the transactions are at least as favorable to the Plans as the terms generally available in arm's-length transactions between unrelated parties. The Equitable Life Assurance Society is the limited partner in the Partnership.

For a more complete statement of the facts and representations supporting the Department's decision to grant this exemption refer to the notice of proposed exemption published on November 23, 1984 at 49 FR 46218.

Effective Date: This exemption is effective July 9, 1984.

For Further Information Contact: Mr. David Stander of the Department, telephone (202) 523–8881. (this is not a toll-free number.)

Austin Oral Surgery Associates Pension Plan and the Austin Oral Surgery Associates Profit Sharing Plan (Collectively, the Plans) Located in Austin, Texas

[Prohibited Transaction Exemption 85–22; Exemption Application Nos. D–5644 and D–5645]

Exemption

The restrictions of section 406(a), 406 (b)(1) and (b)(2) of the Act and the sanctions resulting from the application of section 4975 of the Code, by reason section 4975(c)(1) (A) through (E) of the Code shall not apply to (1) the loans (the Loans) by the Plans of an amount totaling $550,000 to Austin Oral Surgery Associates (the Partnership); and (2) the guarantee of repayment of the Loans by the partners of the Partnership, provided the terms and conditions of both transactions are at least as favorable to the Plans as those obtainable in arm's-length transaction with an unrelated party.

For a more complete statement of the facts and representations supporting the Department's decision to grant this exemption refer to the notice of proposed exemption published on November 2, 1984 at 49 FR 44164.

Effective Date: This exemption is effective December 17, 1984.

Written Comments: The Department received two written comments regarding the notice of proposed exemption. The first comment, submitted by the applicant, indicated the Loans had been entered into on December 17, 1984 and it requested that the exemption be made retroactive to that date. The second comment, submitted by First City National Bank of Austin, which is the trustee of the Plans as well as the independent fiduciary for Plans with respect to the Loans, acknowledged the funding of the Loans on December 17, 1984 and raised no objection to the transactions being entered into before the granting of the exemption.

For Further Information Contact: Ms. Jan D. Broady of the Department, telephone (202) 523–8971. (This is not a toll-free number.)

J. Michael Pisias, Jr., a Professional Corporation Pension Plan (the Plan) Located in San Francisco, CA

[Prohibited Transaction Exemption 85–23; Exemption Application No. D–5679]

Exemption

The sanctions resulting from the application of section 4975 of the Code, by reason of section 4975(c)(1)(A) through (E) of the Code, shall not apply

to the proposed sale by the Plan of a limited partnership interest (the Interest) in Western Mud Co., Limited to J. Michael Pisias, Jr., the trustee of the Plan, provided that the sales price is no less than the fair market value of the Interest at the time the sale is consummated.

For a more complete statement of the facts and representations supporting the Department's decision to grant this exemption refer to the notice of proposed exemption published on December 4, 1984 at 49 FR 47457.

For Further Information Contact: Mr. David M. Cohen of the Department, telephone (202) 523–8671. (This is not a toll-free number.)

Sheboygan Oral and Maxillofacial Associates, Ltd. Defined Contribution Plan (the Plan) Located in Sheboygan, Wisconsin

[Prohibited Transaction Exemption 85–24; Exemption Application No. D–5756]

Exemption

The restrictions of section 406(a), 406(b)(1) and 406(b)(2) of the Act and the sanctions resulting from the application of section 4975 of the Code, by reason of section 4975(c)(1) (A) through (E) of the Code, shall not apply to the proposed sale by the individually directed account of Richard F. Morrissey, M.D. (Dr. Morrissey) in the Plan of five units in the Limited Partnership of Doctors Park Investment Club to Dr. Morrissey for cash in the amount of $34,398.45, provided that such amount is not less than the fair market value of the units on the date of sale.

For a more complete statement of the facts and representations supporting the Department's decision to grant this exemption refer to the notice of proposed exemption published on December 4, 1984 at 49 FR 47459.

For Further Information Contact: Ms. Katherine D. Lewis of the Department, telephone (202) 523–8882. (This is not a toll-free number.)

General Information

The attention of interested persons is directed to the following:

(1) The fact that a transaction is the subject of an exemption under section 408(a) of the Act and/or section 4975(c)(2) of the Code does not relieve a fiduciary or other party in interest or disqualified person from certain other provisions of the Act and/or the Code, including any prohibited transaction provisions to which the exemption does not apply and the general fiduciary responsibility provisions of section 404 of the Act, which among other things require a fiduciary to discharge his duties respecting the plan solely in the interest of the participants and beneficiaries of the plan and in a prudent fashion in accordance with section 404(a)(1)(B) of the Act; nor does it affect the requirement of section 401(a) of the Code that the plan must operate for the exclusive benefit of the employees of the employer maintaining the plan and their beneficiaries;

(2) These exemptions are supplemental to and not in derogation of, any other provisions of the Act and/or the Code, including statutory or administrative exemptions and transitional rules. Furthermore, the fact that a transaction is subject to an administrative or statutory exemption is not dispositive of whether the transaction is in fact a prohibited transaction.

(3) The availability of these exemptions is subject to the express condition that the material facts and representations contained in each application accurately describes all material terms of the transaction which is the subject of the exemption.

Signed at Washington, D.C., this 17th day of January, 1985.

Elliot I. Daniel,

Acting Assistant Administrator for Regulations and Interpretations, Office of Pension and Welfare Benefit Programs, U.S. Department of Labor.

[FR Doc. 85–1731 Filed 1–22–85; 8:45 am]

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NUCLEAR REGULATORY COMMISSION

Monthly Notice; Applications and Amendments To Operating Licenses Involving no Significant Hazards Considerations

1. Background

Pursuant to Public Law (Pub. L.) 97–415, the Nuclear Regulatory Commission (the Commission) is publishing its regular monthly notice. Public Law 97–415 revised section 189 of the Atomic Energy Act of 1954, as amended (the Act), to require the Commission to publish notice of any amendments issued, or proposed to be issued, under a new provision of section 189 of the Act. This provision grants the Commission the authority to issue and make immediately effective any amendment to an operating license upon a determination by the Commission that such amendment involves no significant hazards consideration, notwithstanding the pendency before the Commission of a request for a hearing from any person.

This monthly notice includes all amendments issued, or proposed to be issued, since that date of publication of the last monthly notice which was published on December 31, 1984 (49 FR 50794) through January 14, 1985.

NOTICE OF CONSIDERATION OF ISSUANCE OF AMENDMENT TO FACILITY OPERATING LICENSE AND PROPOSED NO SIGNIFICANT HAZARDS CONSIDERATION DETERMINATION AND OPPORTUNITY FOR HEARING

The Commission has made a proposed determination that the following amendment requests involve no significant hazards consideration. Under the Commission's regulations in 10 CFR 50.92, this means that operation of the facility in accordance with the proposed amendments would not (1) involve a significant increase in the probability or consequences of an accident previously evaluated; or (2) create the possibility of a new or different kind of accident from any accident previously evaluated; or (3) involve a significant reduction in a margin of safety. The basis for this proposed determination for each amendment request is shown below.

The Commission is seeking public comments on this proposed determination. Any comments received with 30 days after the date of publication of this notice will be considered in making any final determination. The Commission will not normally make a final determination unless it receives a request for a hearing.

Comments should be addressed to the Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Docketing and Service Branch.

By February 22, 1985, the licensee may file a request for a hearing with respect to issuance of the amendment to the subject facility operating license and any person whose interest may be affected by this proceeding and who wishes to participate as a party in the proceeding must file a written petition of leave to intervene. Requests for a hearing and petitions for leave to intervene shall be filed in accordance with the Commission's "Rules of Practice for Domestic Licensing Proceedings" in 10 CFR Part 2. If a request for a hearing or petition for leave to intervene if filled by the above date, the Commission or an Atomic Safety and Licensing Board, designated by the Commission by the Chairman of the Atomic Safety and Licensing Board Panel, will rule on the request and/or petition and the Secretary or the designated Atomiv Safety and Licensing

Board will issue a notice of hearing or an appropriate order.

As required by 10 CFR 2.714, a petition for leave to intervene shall set forth with particularity the interest of the petitioner in the proceeding, and how that interest may be affected by the results of the proceeding. The petition should specifically explain the reasons why intervention should be permitted with particular reference to the following factors: (1) The nature of the petitioner's right under the Act to be made a party to the proceeding; (2) the nature and extent of the petitioner's property, financial, or other interest in the proceeding; and (3) the possible efect of any order which may be entered in the proceeding on the petitioner's interest. The petition should also identify the specific aspect(s) of the subject matter of the proceeding as to which petitioner wisher to intervene. Any person who has filed a petition for leave to intervene or who has been admitted as a party may amend the petition without requesting leave of the Board up to fifteen (15) days prior to the first prehearing conference scheduled in the proceeding, but such an amended petition must satisfy the specificity requirements described above.

Not later than fifteen (15) days prior to the first prehearing conference scheduled in the proceeding, a petitioner shall file a supplement to the petition to intervene which must include a list of the contentions which are sough to be litigated in the matter, and the bases for each contention set forth with reasonable specificity. Contentions shall be limited to matters within the scope of the amendment under consideration. A petitioner who fails to file such a supplement which satisfies these requirements with respect to at least one contention will not be permitted to participate as part.

Those permitted to intervene become parties to the proceeding, subject to any limitation in the order granting leave to intervene, and have the opportunity to participate fully in the conduct of the hearing, including the opportunity ot present evidence and cross-examine witnesses.

If a hearing is requested, the Commission will make a final determination on the issue of no significant hazards consideration. The final determination will serve to decide when the hearing is held.

If the final determination is that the amendment request involves on significant hazards consideration, the Commission may issue the amendment and make it immediately effective, notwithstanding the request for a hearing. Any hearing held would take place after issuance of the amendment

If the final determination is that the amendment involves a significant hazards consideration, any hearing held would take place before the issuance of any amendment.

Normally, the Commission will not issue the amendment until the expiration of the 30-day notice period. However, should circumstances change during the notice period such that failure to act in a timely way would result, for example, in derating or shutdown of the facility, the Commission may issue the license amendment before the expiration of the 30-day notice period, provided that its final determination is that the amendment involves no significant hazards consideration. The final determination will consider all public and State comments received before action is taken. Should the Commission take this action, it will publish a notice of issuance and provide for opportunity for a hearing after issuance. The Commission expects that the need to take this action will occur very infrequently.

A request for a hearing or a petition for leave to intervene must be filed with the Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, D.C 20555, Attention: Docketing and Service Branch, or may be delivered to the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C., by the above date. Where petitions are filed during the last ten (10) days of the notice period, it is requested that the petitioner promptly so inform the Commission by a toll-free telephone call to Western Union at (800) 325–6000 (in Missouri (800) 342–6700). The Western Union operator should be given Datagram Identification Number 3737 and the following message addressed to *(Branch Chief):* Petitioner's name and telephone number; date petition was mailed; plant name; and publication date and page number of this **Federal Register** notice. A copy of the petition should also be sent to the Executive Legal Director, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, and to the attorney for the licensee.

Nontimely filings of petitions for leave to intervene, amended petitions, supplemental petitions and/or requests for hearing will not be entertained absent a determination by the Commission, the presiding officer or the Atomic Safety and Licensing Board designated to rule on the petition and/or request, that the petitioner has made a substantial showing of good cause for the granting of a late petition and/or request. That determination will be based upon a balancing of the factors specified in 10 CFR 2.714(a)(1)(i)–(v) and 2.714(d).

For further details with respect to this action, see the application for amendment which is available for public inspection at the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C., and at the local public document room for the particular facility involved.

Boston Edison Company, Docket No. 50–293, Pilgrim Nuclear Power Station, Plymouth, Massachusetts

Date of amendment request: October 16, 1984.

Description of amendment request: The proposed amendment requests modification of the Technical Specifications to reflect changes in the reporting requirements outlined in 10 CFR 50.72 and 50.73 and guidance provided in the Commission's Generic Letter 83–43. Specifically, the Technical Specifications would be modified as follows:

1. The term "reportable occurrence" would be replaced by "reportable event."

2. Section 6.9.B entitled, "Reportable Occurrences," would be removed. Since the removal of this entire section would eliminate a requirement, unrelated to operating events, to report changes in the licensee's organization, that requirement would be moved to Section 6.2, "Organization."

3. The reference in Section 6.6.A to the "requirements of Specification 6.9" would be changed to "requirements of either 10 CFR 50.72 or 10 CFR 50.73."

4. A time of one hour for reporting a safety limit violation would be added to Section 6.7.B.

5. A time limit of 30 days for submitting a safety limit violation report would be added to Section 6.7.D.

6. Section 6.5.B.7.g would be changed to require the licensee's Nuclear Safety Review and Audit Committee to review "all events which are required by 10 CFR 50.73 to be reported to the NRC in writing."

7. Section 3.9.B.2 would be changed to require NRC notification within one hour after incoming power is not available from both startup and shutdown transformers and reactor operation is continuing under certain permissible conditions.

8. Reporting requirements would be deleted from Section 3.6.D.3, 3.9.B.1, 3.9.B.4 and 3.9.B.5.

Basis for proposed no significant hazards consideration determination: The Commission has provided guidance for the application of the standards in 10

CFR 50.92 by providing certain examples (48 FR 14870) of actions likely to involve no significant hazards considerations. One of these is example "(vii) A change to make a license conform to change in the regulations where the license change results in very minor changes to facility operations clearly in keeping with the regulations." This example applies to the proposed amendment since it is intended to conform to changes in the regulations which have little, if any, effect on facility operation.

Since the application for amendment involves changes which are similar to examples for which no significant hazards consideration exists, the staff has made a proposed determination that the application involves no significant hazards consideration.

Local Public Document Room location: Plymouth Public Library, North Street, Plymouth, Massachusetts 02360.

Attorney for licensee: W.S. Stowe, Esq., Boston Edison Company, 800 Boylston Street, 36th Floor, Boston, Massachusetts 02199.

NRC Branch Chief: Domenic B. Vassallo.

Boston Edison Company, Docket No. 50–293, Pilgrim Nuclear Power Station, Plymouth, Massachusetts

Date of amendment request: November 9, 1984.

Description of amendment request: The amendment would change the Administrative Controls Section of the Technical Specifications as follows:

1. The title "Station Manager" becomes "Nuclear Operations Manager."

2. A new position entitled "Technical Station Head" is established to oversee the On-site Safety and Performance Group and the Technical Group at the plant. This new position will report to the Nuclear Operations Manager and will assume from him the responsibility of Chairman of the Operations Review Committee (ORC).

3. A new position entitled "Chief Chemical Engineer" and a chemistry technical staff are established. The person in this position will report to the Nuclear Operations Manager and will be a member of ORC.

4. Alternate members of ORC to serve on a temporary basis would be appointed by the Nuclear Operations Manager instead of the ORC Chairman.

5. An addition is made to the statement of authority for ORC to clarify that it can recommend proposals related to nuclear safety or reject those which do not satisfy the Committee's concerns.

Basis for proposed no significant hazards consideration determination: The proposed changes are all administrative improvements designed to increase the effectiveness of the station personnel. Their responsibilities for maintaining plant safety are not diminished and the changes will not physically affect any safety related systems. The staff, therefore, proposes to conclude that the license amendment would not (1) involve a significant increase in the probability or consequences of an accident previously evaluated, (2) create the possibility of an accident of a type different from any previously evaluated, or (3) involve a significant reduction in a margin of safety. On this basis, the staff has made an initial determination that the proposed amendment is not likely to involve significant hazards considerations.

Local Public Document Room location: Plymouth Public Library, North Street, Plymouth, Massachusetts 02360.

Attorney for licensee: W.S. Stowe, Esq., Boston Edison Company, 800 Boylston Street, 36th Floor, Boston, Massachusetts 02199.

NRC Branch Chief: Domenic B. Vassallo.

Commonwealth Edison Company, Docket No. 50–265, Quad Cities Nuclear Power Station, Unit 2, Rock Island County, Illinois

Date of amendment request: December 4, 1984.

Description of amendment request: This amendment would increase the Technical Specification limit on the linear heat generation rate (LHGR) for sixteen Barrier Fuel Test Assemblies in the Barrier Fuel Demonstration Program from 13.4 kw/ft to 15.0 kw/ft for the remainder of the current Operating Cycle 7. The purpose of the change is to enable the licensee to properly perform a control rod withdrawal ramp test at the end of Cycle 7 without exceeding the current LHGR limits.

Basis for proposed no significant hazards consideration determination: The licensee's submittal of December 4, 1984 contains an evaluation of the proposed action, and a basis for a proposed no significant hazards consideration determination. The licensee's proposed determination is based on the following considerations.

The criteria for defining a significant hazards consideration is set forth in 10 CFR 50.92(c). Applying these criteria to the proposed action, operation of Quad Cities Unit 2 in accordance with the proposed amendment, would not:

(1) Involve a significant increase in the probability or consequences of an accident previously evaluated because adequate margin to the 1% plastic strain limit is maintained for the worst case transient described in the Final Safety Analysis Report (FSAR).

(2) Create the possibility of a new or different kind of accident from any accident previously evaluated because the proposed Technical Specification does not allow any new modes of operation beyond that normally performed at operating boiling water reactors (BWRs).

(3) Involve a significant reduction in the margin of safety because a 4.8 kw/ft (or greater) margin to the 1% plastic strain limit exists for the worst case transient described in the FSAR.

Additionally, this request is of a type which was specifically cited in the **Federal Register** (48 FR 14870) as an example of license amendment not involving significant hazards and therefore not requiring opportunity for prior hearings. That is:

> (vi) A change which either may result in some increase to the probability or consequences of a previously analyzed accident or may reduce in some way a safety margin, but where the results of the change are clearly within all acceptable criteria with respect to the system or component specified in the Standard Review Plan.

The staff has reviewed the licensee's significant hazards consideration determination and, based upon this reviewed, the staff has made a proposed determination that the application for amendment involves no significant hazards consideration.

Local Public Document Room location: Moline Public Library, 504–17th Street, Illinois 61265.

Attorney for licensee: Mr. Robert G. Fitzgibbons, Jr., Isham, Lincoln, & Beale. Three First National Plaza, Suite 5200. Chicago, Illinois 60602.

NRC Branch Chief: Domenic B. Vassallo.

Consumers Power Company, Docket No. 50–255, Palisades Plant, Van Buren County, Michigan

Date of amendment request: October 25, 1984.

Description of amendment request: The proposed amendment would: (1) Correct a statement in the Technical Specifications that identifies which waste gas decay tank is to be chosen for release to minimize the amount of radioactivity being released, and (2) correct the setpoint specified in the Technical Specifications for the High Range Noble Gas Monitor, Main Steam Safety and Dump Valve Discharge Line Monitor and Engineered Safeguards Room Vent System Monitor.

Basis for proposed no significant hazards consideration determination: The Commission has provided guidance

concerning the application of the standards in 10 CFR 50.92 by providing certain examples (48 FR 14870, April 6, 1983). One of the examples (i) of actions not likely to involve a significant hazards consideration relates to purely administrative changes to the Technical Specifications such as corrections of errors. The proposed change (1) above is needed to correctly identify the waste gas decay tank with the least radioactivity for releasing and change (2) above will correct the setpoint setting for those monitors which are used for monitoring potential high level releases after an accident. The setpoints were erroneously specified at the low levels for routine releases.

Therefore, because this amendment request involves administrative changes of the types specified in example (i) of the Commission's guidance, the staff proposes to determine that the proposed changes would not involve a significant hazards consideration.

Local Public Document Room location: Kalamazoo Public Library, 315 South Rose Street, Kalamazoo, Michigan 49007.

Attorney for licensee: Judd L. Bacon, Esquire, Consumers Power Company, 212 West Michigan Avenue, Jackson, Michigan 49201.

NRC Branch Chief: John A. Zwolinski.

Duke Power Company, Dockets Nos. 50-269, 50-270, and 50-287, Oconee Nuclear Station, Units Nos. 1, 2 and 3, Oconee County, South Carolina

Date of amendment request: December 19, 1984.

Description of amendment request: The proposed amendments would revise the Technical Specifications (TSs) to support the operation of Oconee Unit 2 at full rated power during the upcoming Cycle 8. The proposed amendment request changes the following areas:

1. Rod Position Limits (TS 3.5.2); and
2. Power Imbalance Limits (TS 3.5.2).

To support the license amendment request for operation of Oconee Unit 2 during Cycle 8, the licensee submitted, as an attachment to the application, a Duke Power Company (DPC) Report, DPC-RD-2004, "Oconee Unit 2, Cycle 8 Reload Report." A summary of the Cycle 8 operating parameters is included in the report, along with safety analyses.

During the refueling outage, 109 fuel assemblies will be reinserted, similar to those previously used, and 68 fuel assemblies will be discharged and replaced by new but substantially similar assemblies of the Mark BZ type. Additionally, Cycle 8 will incorporate gray (less-absorbing) axial power shaping rods (APSRs) instead of the previously used black (highly-absorbing) APSRs.

Basis for proposed no significant hazards consideration determination: The Commission has provided guidance concerning the application of the standards in 10 CFR 50.92 by providing certain examples (48 FR 14870). Example (iii) of the types of amendments not likely to involve significant hazards considerations is an amendment to reflect a core reload where:

(1) No fuel assemblies significantly different from those found previously acceptable to the Commission for a previous core at the facility in question are involved;

(2) No significant changes are made to the acceptance criteria for the Technical Specifications;

(3) The analytical methods used to demonstrate conformance with the Technical Specifications and regulations are not significantly changed; and

(4) The NRC has previously found such methods acceptable.

This particular reload involves the reinsertion of 109 fuel assemblies of a type previously approved and used and the insertion of 68 fuel assemblies of the Mark BZ type. The Mark BZ fuel assemblies are the same as previously approved assemblies in terms of fuel rods, end grid, end fittings, and guide tubes and differ only slightly in the use of Zircaloy spacer grids rather than Inconel Intermediate Spacer grids. The use of the Mark BZ fuel assembly has been previously reviewed and approved by the Commission.

The Cycle 8 control rods differ from those of Cycle 7 in that gray APSRs are to be utilized instead of the previously used black APRSs. The gray APSRs have a grater absorber length than the APRSs used in previous reloads and utilize an Inconel absorber instead of the Ag-In-Cd alloy. According to the analyses described in DPC-RC-2004, "Oconee Unit 2, Cycle 8 Reload Report," the gray APSRs will not adversely affect Cycle 8 operation. The Commission has previously approved the use of gray APSRs.

Thus, this core reload involves the use of fuel assemblies and control rods that are not significantly different from those found previously acceptable to the Commission for a previous core at this facility. The request for amendment changes the TSs to reflect new operating limits based on the fuel and control rods to be inserted into the core. These parameters are based on the new physics of the core and fall within the acceptance criteria.

In the analyses supporting this reload, there have been no significant changes in acceptance criteria for the Technical Specifications, the analytical methods used to demonstrate conformance with the Technical Specifications and the regulations were not significantly changed, and those analytical methods have previously been found acceptable. Thus, this reload and the proposed license amendments reflecting it appear to be encompassed by example (iii) of amendments not likely to involve significant hazards considerations. On this basis, the Commission proposes to determine that these amendments do not invovle significant hazards considerations.

Local Public Document Room location: Oconee County Library, 501 West Southbroad Street, Walhalla, South Carolina.

Attorney for licensee: J. Michael McGarry, III, Bishop, Liberman, Cook, Purcell and Reynolds, 1200 Seventeenth Street NW., Washington, D.C. 20036.

NRC Branch Chief: John F. Stolz.

Duquesne Light Company, Docket No. 50-334, Beaver Valley Power Station, Unit No. 1, Shippingport, Pennsylvania

Date of amendment request: November 4, 1984.

Description of amendment request: This is an application for an amendment to Operating License DPR-66, revising the Technical Specifications to reflect the flow assumptions used for the postulated rod bank withdrawal accident in the Updated Final Safety Analysis Report. The assumed flow during Mode 3, hot shutdown, is ensured by use of two of the three operating reactor coolant loops. Currently, the specifications require only one loop be in operation for Mode 3. The proposed change would require that two loops be in operation for Mode 3.

Basis for proposed no significant hazards consideration determination: The Commission has provided guidance concerning the application of these standards by providing certain examples (48 FR 14870). One of these, Example (ii), involving no significant hazards considerations is "A change that constitutes an additional limitation, restriction, or control not presently included in the technical specifications: for example, a more stringent surveillance requirement." The requested change matches the example and the staff, therefore, proposes to characterize it as involving no significant hazards consideration.

Local Public Document Room location: B. F. Jones Memorial Library, 663 Franklin Avenue, Aliquippa, Pennsylvania 15001.

Attorney for licensee: Gerald Charnoff, Esquire, Jay E. Silberg,

Esquire, Shaw, Pittman, Potts, and Trowbridge, 1800 M Street NW., Washington, D.C. 20036.

NRC Branch Chief: Steven A. Varga.

Indiana and Michigan Electric Company, Docket Nos. 50–315 and 50–316, Donald C. Cook Nuclear Plant, Unit No. 2, Berrien County, Michigan

Date of amendment request: December 3, 1984.

Description of amendment request: The proposed amendment would make changes to the Technical Specifications for D. C. Cook Nuclear Plant Unit Nos. 1 and 2 to require at least two reactor coolant loops be in operation during mode 3 unless the reactor trip breakers were disconnected and to require at least one reactor coolant loop be in operation if the reactor trip breakers are disconnected.

Basis for proposed no significant hazards consideration determination: The Commission has provided guidance concerning the application of the standards in 10 CFR 50.92 by providing certain examples (48 FR 14870, April 6, 1983). One of the examples (i) of an action not likely to involve a significant hazards consideration is a purely administrative change to technical specifications for example, a change to achieve consistency throughout the technical specifications, correction of an error, or a change in nomenclature. The proposed change is like this example in that the Final Safety Analysis Report was prepared and reviewed on the basis of two reactor coolant loops in operation during mode 3 unless the reactor trip breakers were disconnected and then only one loop need be in operation. The original Technical Specifications incorrectly requires only one loop be in operation in mode 3, hot standby. The proposed change is to correct the error in the Technical Specifications. On the basis of the above, the Commission proposes to conclude that the proposed changes involves a no significant hazards consideration.

Local Public Document Room location: Maude Reston Palenske Memorial Library, 500 Market Street, St. Joseph, Michigan 49085.

Attorney for licensee: Gerald Charnoff, Esquire, Shaw, Pittman, Potts and Trowbridge, 1800 M Street NW., Washington, D.C. 20036.

NRC Branch Chief: Steven A. Varga.

Pennsylvania Power & Light Company, Docket No. 50–387, Susquehanna Steam Electric Station, Unit 1, Luzerne County, Pennsylvania

Date of amendment request: October 31, 1984.

Description of amendment request: The purpose of the amendment is to request a change in the Unit 1 Technical Specifications Table 3.3.2–2. The licensee is proposing that the setpoint for MSIV isolation on reactor vessel water level be changed from Level 2 to Level 1 in order to reduce the number of challenges to the Safety Relief Valves (SRV). The change is consistent with the NRC recommendations in Item 16 of NUREG–0737 Section II.K.3, "Reduction of Challenges and Failures of Relief Valves—Feasibility Study and System Modification."

Basis for proposed no significant hazards consideration determination: The licensee in his letter dated October 31, 1984, stated that the proposed change does not: (1) Involve a significant increase in the probability or consequences of an accident previously evaluated, (2) create the possibility of a new or different kind of accident from any accident previously evaluated, or (3) involve a significant reduction in margin of safety. The NRC staff agrees with the licensee's evaluation in this regard and proposes to find the proposed changes to Technical Specification Table 3.3.2–2 involve no significant hazards consideration. The Commission has provided guidance concerning the application of the no significant hazards consideration standards by providing certain examples (48 FR 14870). One of the examples of actions not likely to involve a significant hazards consideration, example (vi), is a change which either may result in some increase to the probability or consequences of a previously-analyzed accident or may reduce in some way a safety margin, but where the results of the change are clearly within all acceptable criteria with respect to the system or component specified in the Standard Review Plan: For example, a change resulting from the application of a small refinement of a previously used calculational model or design method. The change to Table 3.3.2–2 may constitute a reduction in some way of the safety margin, but is still within all acceptable criteria with respect to the system or component. Therefore, the proposed change is encompassed by this example and on that basis the NRC staff proposes to find this proposed change does not involve a significant hazards consideration.

Local Public Document Room location: Osterhout Free Library, Reference Department, 71 South Franklin Street, Wilkes-Barre, Pennsylvania 18701.

Attorney for licensee: Jay Silberg, Esquire, Shaw, Pittman, Potts & Trowbridge, 1800 M Street NW., Washington, D.C. 20036.

NRC Branch Chief: A. Schwencer.

Pennsylvania Power & Light Company, Docket No. 50–387, Susquehanna Steam Electric Station, Unit 1, Luzerne County, Pennsylvania

Date of amendment request: November 13, 1984.

Description of amendment request: The purpose of the amendment request is to propose changes to the Susquehanna Steam Electric Station Unit 1 Technical Specification to incorporate the changes necessary to support the plant modifications required to comply with License Condition 2.C.(17)(b)(2). The changes proposed in Tables 2.2.1–1, 3.3.1–1, 3.3.1–2, and 4.3.1.1–1 reflect the addition of a level transmitter to indicate Scram Discharge Volume Water Level-High. Previously only a float switch was used for indication. In Table 3.3.6–1 the proposed change imposes an additional restriction by increasing the minimum number of operable channels necessary per trip function from one to two. The final proposed change on page 3/4 8–33 is administrative in nature. The addition of footnote ** "Initial setpoint. Final setpoint to be determined during startup testing following the first refueling outage. Any required change to this setpoint shall be submitted to the Commission within 90 days of test completion" allows the licensee to verify through testing the previously calculated setpoint and correct the calculated value if necessary. This change clarifies the fact that the setpoint contained in the technical specifications is a calculated value requiring verification through testing.

Basis for proposed no significant hazards consideration determination: The licensee in his letter dated November 13, 1984, proposed that the modifications do not involve a significant hazards consideration. The Commission has provided guidance concerning the application of the no significant hazards consideration standards by providing certain examples (48 FR 14870). One of the examples of actions not likely to involve a significant hazards consideration, example (ii) involves a change that constitutes an additional limitation, restriction, or control not presently included in the technical specifications: For example, a more stringent surveillance requirement. All the proposed technical specification changes except for the last constitute an additional limitation and, thus, fall within example (ii) of actions not likely

to involve significant hazards considerations. The last proposed change is administrative and therefore example (i)–a purely administrative change to technical specifications: For example, a change to achieve consistency throughout the technical specifications, correction of an error, or a change in nomenclature—applies. Based on the above discussion the NRC staff proposes to find that the above changes do not involve a significant hazards consideration.

Local Public Document Room Location: Osterhout Free Library, Reference Department, 71 South Franklin Street, Wilkes-Barre, Pennsylvania 18701.

Attorney for licensee: Jay Silberg, Esquire, Shaw, Pittman, Potts & Trowbridge, 1800 M Street NW., Washington, D.C. 20036.

NRC Branch Chief: A. Schwencer.

Philadelphia Electric Company, Public Service Electric and Gas Company, Delmarva Power and Light Company, and Atlantic City Electric Company, Docket No. 50–277, Peach Bottom Atomic Power Station, Unit No. 2, York County, Pennsylvania

Date of amendment request: September 7, 1984.

Description of amendment request: The proposed amendment would revise the Unit 2 Technical Specifications to: (1) Establish operating limits for all fuel types for the upcoming Cycle 7 operation; (2) establish the Maximum Average Planar Linear Heat Generation Rate (MAPLHGR) for all fuel types for Cycle 7 operation; (3) permit operation with hafnium (General Electric Hybrid I) control rods; (4) modify bases to delete reference to specific shutdown margin provided by Stanby Liquid Control System to reduce need for future cycle dependent revisions; and (5) modify that MAPLHGR reduction function for single loop operation. These changes were proposed in connection with the Cycle 7 refueling outage for Unit 2.

Basis for proposed no significant hazard consideration determination: The requested amendment to the Peach Bottom Atomic Power Station, Unit 2, operating license is being submitted in support of the upcoming Cycle 7 core reload. The requested amendment will incorporate Technical Specification (TS) changes as diescussed in the evaluation accompanying the licensee's application. The Cycle 7 core design would require the loading of 292 new fuel assemblies, approximately one-third of the reactor core. The new fuel assemblies are similar to the other fuel assemblies in the core except for the addition of barrier cladding used to reduce cladding failures due to pellet clad interaction. The proposed TSs would also change: (1) The operating limit minimum critical power ratio (MCPR) values for all fuel types for Cycle 7 operation; and (2) would incorporate the maximum average planar linear heat generation rate (MAPLHGR) versus planar average exposure curves for the new fuel assemblies. The Commission has provided guidance for determining whether a proposed amendment involves a significant hazards consideration (48 FR 14870). An example of an amendment that is not likely to involve a significant hazards consideration is "(iii) * * *, a change resulting from a nuclear reactor core reloading, if no fuel assemblies significantly different from those found previously acceptable to the NRC for a previous core at the facility in question are involved. This assumes that no significant changes are made to the acceptance criteria for the technical specifications, that the analytical methods used to demonstrate conformance with the technical specifications and regulations are not significantly changed, and the NRC has previously found such methods acceptable".

The Commission's staff considers the above two changes to be similar to example (iii) because the staff has previously reviewed the barrier cladding fuel design and found that the addition of the Zirconium liner to the cladding does not result indifferent operating characteristics or safety margins from those of the non-barrier fuel. The proposed change in the operating limit MCPR causing a reduction in values will not decrease the safety margin because the core loading Cycle 7 refueling is such that calculations indicate that transients would be milder than those of the previous cycle and would result in small changes in the MCPR values. Thus, the probability of reaching the safety limit MCPR during operation is not increased. No changes in the previously accepted analytical methods used to demonstrate conformance with the Technical Specifications and regulations are involved. Therefore, no significant difference in safety to the public is expected from substituting the barrier cladding fuel for some of the non-barrier fuel that has been used during previous cycles or from slightly reducing the operating limit MCPR values.

The third proposed change would reflect the use of the hybrid design hafnium control rod assemblies. These assemblies will be used to replace standard control rod assemblies during the Unit 2 refueling outage. The Hybrid I Control Rod (HICR) Assemblies have been designed by General Electric (GE) to be used as direct replacement for the present control rod assemblies. The original control rods contained only boron carbide, B_4C, as the absorbing material. The new assembly design uses B_4C absorber cubes and three solid hafnium rods in the outside edge wing. This new design will lengthen control rod lifetime.

The description of these control rods was submitted to the NRC by General Electric in topical report NEDE–22290. Based on the staff's evaluation of the information provided in (a) NEDE–22290, (b) a meeting with GE representatives, and (c) responses to NRC staff questions, the staff concluded that there is reasonable assurance that the substitution of Type I HICRs for other approved GE control rod blades will not result in unacceptable hazards to the public and should, in fact, result in improved control blade performance and a positive contribution to reactor safety.

A proposed amendment to an operating license for a facility involves no significant hazards consideration if operation of the facility in accordance with the proposed amendment would not (1) involve a significant increase in the probability or consequences of an accident previously evaluated; or (2) create the possibility of a new or different kind of accident from any previously evaluated; or (3) involve a significant reduction in a margin of safety. The staff has reviewed the proposed change and the related topical report. The licensee concludes that the proposed change does not involve a significant hazards consideration, and based on the following discussion, the staff concur with the conclusion.

The materials evaluation, which includes the chemical, physical, mechanical and irradiation properties, indicates that data and experience demonstrate acceptable corrosion resistance in high temperature water and steam for hafnium in BWR control rods. The physical properties expected to be germane to control applications indicate acceptable performance in the BWR environment.

The mechanical evaluation indicates that the thermal expansion and irradiation growth of hafnium will not interfere with the velocity limiters.

A nuclear evaluation indicates that the HICR will have no significant impact on core and fuel operation when used as a replacement for the current B_4C control rod assemblies. Experiments

provide critical benchmarks for calculations and illustrate a minimum impact on local power and flux distributions with all hafnium rods. An even smaller impact is expected for HICR which is a mixture of hafnium and B_4C. Therefore, the HICR can be used without change in the current rod assemblies and current design procedures.

Thermal-hydraulic evaluation shows that the maximum temperature of the new rods is not significantly different from the currently used control rod assemblies.

An accident evaluation shows that the HICR weight and envelope are identical to the current assemblies. The mechanical and nuclear properties of the HICR do not differ from the current asssemblies in any measures that might be significant during normal or accident conditions. The HICR is, except for minor differences, mechanically identical to the BWR assemblies for which many reactor years of safe operating experience are available. Accordingly, the mechanical safety analysis for the HICR is enveloped by the mechanical safety analyses for the current assemblies.

The reactor core response for the HICR design has been evaluiated against the current control rod design for comparison with linear heat generation, minimum critical power ratio and maximum average planer heat generation limits. The HICR weight and rod worth are the same as the current rod design, therefore the scram speed and scram reactivity are the same, and the above limits are not affected by the change.

Based on the above, the staff has determined that: (1) the probability of occurence or the consequences of an accident would not be increased above those analyzed in the Final Safety Analysis Report (FSAR) because the weight and envelope of the HICR are identical to those of the currently used assemblies, and the nuclear and mechanical properties of the HICR do not differ from currently used assemblies in a significant way; (2) the possibility of an accident different from those analyzed in the FSAR would not result from these changes because, in addition to the above, these systems would not be operated in manner new or different from that described in the FSAR; and (3) the margin of safety provided by Technical Specifications would not be reduced because the proposed change involves no significant relaxation of the criteria used to establish safety limits, no significant relaxation of the bases for limiting safety system settings, and no signficant relaxation in limiting conditions for operation. Therefore, the staff finds that operation of the facility in accordance with the above proposed change would not: (1) Involve a significant increase in the probability or consequences of an accident previously evaluated; (2) create the possibility of a new or different kind of accident; (3) involve a significant reduction in a margin of safety.

The fourth proposed change would delete from the Bases of the Peach Bottom Unit 2 TSs reference to a specific numerical shutdown margin (SDM) provided by the Standby Liquid Control System (SLCS) The SLCS capability is providied as part of the standard Peach Bottom Reload Supplement and is routinely reviewed by the NRC staff. The licensee states that this proposed change is in accordance with the NRC approved reload licensing procedures ("General Electric Standard Application for Reactor Fuel", General Electric Report NEDE–24011–P–A). The staff had previously approved a similar requested change as part of the Peach Bottom Unit 3 reload.

Based on the above, the staff has determined that: (1) The probability of occurrence or the consequences of an accident would not be increased above those previously evaluated because the actual value of the SDM will be provided and available for staff review for each refueling cycle as part of the supplemental reload licensing submittals addressing the 660 parts per million of boron which is cited in the Bases to the Peach Bottom TSs; (2) the possibility of a new or different kind of accident from any accident previously evaluated would not result from this change because the TS requirement for the SLCS to bring the reactor from full power down to a subcritical condition would not be changed by this action; and (3) the margin of safety provided by the TSs would not be reduced because the proposed change in the Bases would not change the capability of the SLCS to bring the reactor, at any time in a fule cycle, from full power and minimum control rod inventory to a subcritical condition with the reactor in the most reactive xenon-free state.

Finally, the amendment request would modify the MAPLHGR reduction factor for single loop operation (SLO) based upon the safety analyses for single loop operation provided in the GE Document NEDO–24229–1, June 1984. The licensee, as part of this reload analysis, checked the MAPLHGR reduction factors for SLO because of the introduction of the new barrier cladding fuel types discussed above. Based upon this review and reanalysis, a slight modification in reduction factor has been proposed in order to maintain the validity of the NRC approved SLO analysis. This change is a part of the reload analysis as discussed above. Since the new fuel assemblies are not significantly different from those found previously acceptable to the NRC for previous core reloads at this facility, and since no significant changes have been made to the acceptance criteria for the TSs by this change, and since the analytical methods used to demonstrate conformance with the TSs and regulations are not significantly changed by this action, and since the NRC has previously found such methods acceptable, the staff, therefore, has determined that the above fits example (iii) (referenced above) of a change not likely to involve a significant hazards consideration.

Since the amendment involves proposed changes for which no significant hazards considerations exists, the staff has made a proposed determination that this application for amendment involves no significant hazards consideration.

Local Public Document Room Location: Government Publication Section, State Library of Pennsylvania, Education Building, Commonwealth and Walnut Streets, Harrisburg, Pennsylvania.

Attorney for licensee: Troy B. Conner, Jr., 1747 Pennsylvania Avenue, NW., Washington, D.C. 20006.

NRC Branch Chief: John F. Stolz.

Public Service Electric and Gas Company, No. 50–311, Salem Nuclear Generating Station, Unit No. 2, Salem County, New Jersey

Date of amendment request: March 27, 1984.

Description of amendment request: The proposed change would revise appropriate portions of the INDEX, DEFINITIONS, and ADMINISTRATIVE CONTROLS sections of Appendix A to the Technical Specifications, as attached, to reflect recent revisions to § 50.72 and the addition of § 50.73 to Title 10 of theCode of Federal Regulations which became effective on Janury 1, 1984.

Specifically § 50.73 states that: "The requirements contained in this section replace all existing requirements for licensees to report 'Reportable Occurrences' as defined in individual plant Technical Specifications", the reporting requirements incorporated into the "Administrative Controls" section of the Salem technical specifications would be changed to reflect the revised reporting requirements; the definition, "Reportable Occurrence" would be

replaced by a new term, "Reportable Event"; and, the Index would be updated.

Basis for proposed no significant hazards consideration determination: The Commission has provided guidance concerning the application of the Standards for a No Significant Hazards determination by providing examples of actions not likely to involve a Significant Hazards Consideration in the **Federal Register** (48 FR 14870). One of the examples (vii) relates to changes that make a license conform to changes in the regulations, where the license change results in very minor changes to facility operations clearly in keeping with the regulations.

Based on the above, and since the proposed change involves actions that conform to the referenced example in 48 FR 14870, we have determined that this application for amendment involves no Significant Hazards Consideration.

Local Public Document Room location: Salem Free Library, 122 West Broadway, Salem, New Jersey 08079.

Attorney for licensee: Conner and Wetterhann, Suite 1050, 1747 Pennsylvania Avenue NW., Washington, D.C. 20006.

NRC Branch Chief: Steven A. Varga.

Rochester Gas and Electric Corporation, Docket No. 50–244, R. E. Ginna Nuclear Power Plant, Wayne County, New York

Date of amendment request: December 1, 1983, as supplemented July 31, 1984.

Description of amendment request: This amendment would grant a one time exception to the requirements of section 4.4.4.1(d) of the Ginna Technical Specifications (TS). Section 4.4.4.1(d) requires that visual inspection of all containment tendons be done if more than 20 wires (out of the 14 tendons selected for inspection) have been broken since the last inspection.

Basis for proposed no significant hazards consideration determination: During July 1983, a scheduled containment tendon surveillance was undertaken by the licensee. A total of 18 tendons were to be visually inspected as well as undergo stress surveillance. The inspection of the first 12 tendons revealed no broken wires and no other anomalies. The lift-off tests showed that all tendon forces exceeded the TS minimum values.

Following the testing of the 12th tendon, the test equipment prematurely disengaged from the tendon head coupling causing damage to the components. An inspection conducted after the incident revealed that 24 of the 90, ¼-inch diameter steel wires were broken. Section 4.4.4.1(d) of the TS requires that all 160 tendons be inspected if more than 20 wires in 14 tendons are found to be broken since the last surveillance inspection.

The licensee requested an exception from this requirement for the following reasons:

(1) The intital inspection of tendon no. 75 and the other 11 tendons revealed no broken wires prior to the incident.

(2) The cause of the broken wires is attributable to the stressing equipment failure and not due to an unexplainable loss of tendon integrity.

(3) Adherence to the technical specifications would involve degreasing the tendon heads prior to conducting an inspection. The casing filler covering the tendon heads is a stiff, putty-like substance making degreasing operations a time-consuming orderal.

(4) Subsequent visual inspection of the four adjacent tendons in accordance with TS 4.4.4.1(e) revealed no broken wires.

(5) Subsequent lift-off testing of two of the four adjacent tendons yielded lift-off forces of 701 kips and 724 kips. Although predicitions are not available for these tendons, the results are within the range of other tendon forces, thus indicating that no significant change in lift-off force occurred in adjacent tendons.

No broken wires were found in the tendon inspection preceding the accident nor in the inspection of the remaining seven. The strength of the damaged tendon, not withstanding the loss of 24 of its 90 wires, proved to be compatible with the other adjacent tendons. Despite the damage to one tendon the calculated average force level of all the the tendons in the containment exceeds the minimum value required by the TS by 11.2 percent.

The Commission has provided guidance concerning the application of standards of no significant hazards consideration by providing certain examples (April 6, 1983, 48 FR 14870). These examples are not applicable to the proposed request. Accordingly, the question of no significant hazards consideration will be determined solely by the standards. The basis for concluding that the standards are met with respect to a no significant hazards consideration is presented below.

First Standard: Amendment does not significantly increase the probability or consequences of an accident previously evaluated. The wires were broken as the result of an accident, not through unknown deterioration. Further, the average force level of all of the containment tendons exceeds the minimum value required by the TS. Adequacy of the tendons has thus been verified and a one-time exception from the further inspection requirements of section 4.4.4.1(d) of the TS does not involve a significant increase in the probability or consequences of an accident previously evaluated.

Second Standard: Amendment does not create the possibility of a new and different accident from any previously evaluated. The TS provide for additional inspections where there is damage to tendon wires from unknown causes. The requested one-time exception from additonal inspections where the cause of tendon wire damage is known and makes further inspections unnecessary does not create the possibility of a new or different kind of accident from any accident previously evaluated.

Third Standard: Amendment does not significantly reduce a safety margin. The average force of all of the tendons is above the required minimum. Granting the requested exception from further inspection will not affect that force or otherwise affect tendon integrity and thus will not involve a significant reduction in a margin of safety.

Because the standards of 10 CFR 50.92 have been met, the Commission proposes to determine that the application does not involve a significant hazards consideration.

Local Public Document Room location: Rochester Public Library, 115 South Avenue, Rochester, New York 14604.

Attorney for licensee: Harry H. Voigt, Esquire, LeBoeuf, Lamb, Leiby and MacRae, 1333 New Hampshire Avenue NW., Suite 1100, Washington, D.C. 20036.

NRC Branch Chief: John A. Zwolinski, Chief.

Sacramento Municipal Utility District, Docket No. 50–312, Rancho Seco Nuclear Generating Station, Sacramento County, California

Date of amendment request: May 30, 1984.

Description of amendment request: This submittal supplements the request for amendment dated October 27, 1980, which was noticed in the **Federal Register** on December 21, 1983 (48 FR 56509). The submittal provides additional information supplementing the information in the October 27, 1980, submittal on the additional requirements proposed to ensure that proper means are available to provide redundant methods of decay heat removal. The Technical Specification revisions proposed in the October 27, 1980, application remain unchanged.

Basis for proposed no significant hazards consideration determination: The Commission has provided guidance

concerning the application of the standards for a no significant hazards determination by providing certain examples (48 FR 14870). One of the examples (ii) of actions not likely to involve a significant hazards consideration relates to changes that constitute additional restrictions or controls not presently included in the Technical Specifications.

The May 30, 1984, submittal provides additional technical information to supplement the information in the submittal of October 27, 1980. The supplemental information does not change the proposed Technical Specifications. Therefore, our previous proposed determination that the proposed change does not involve a significant hazards consideration since it consists of an additional limitation on the operation of the facility not currently in the Technical Specifications remains unchanged.

Local Public Document Room location: Sacramento City-County Library, 828 I Street, Sacramento, Claifornia.

Attorney for licensee: David S. Kaplan, Sacramento Municipal Utility District, 6201 S Street, P.O. Box 15830, Sacramento, California 95813.

NRC Branch Chief: John F. Stolz.

Southern California Edison Company, Docket No. 50–206, San Onofre Nuclear Generating Station, Unit No. 1, San Diego County, California

Date of amendment request: November 30, 1984.

Description of amendment request: This submittal is a revision to the request for amendment dated July 17, 1984 which was noticed in the monthly **Federal Register** notice on August 22, 1984 (49 FR 33373). This revision clarifies the July 17, 1984 submittal in response to the NRC's letter dated September 5, 1984. This amendment would approve changes to the Technical Specifications to include the requirement to limit the amount of overtime worked by plant staff members performing safety-related functions.

Basis for proposed no significant hazards consideration determination: Generic Letter 82–16 requested all Pressurized Water Power Reactor Licensees to review their Technical Specifications to determine if they were consistent with the guidance provided in the generic letter. For items where utilities identified deviations or the absence of a specification, they were requested to submit an application for a license amendment. In response to that request, the licensee for San Onofre 1 determined that there are no provisions in the Technical Specifications that address plant staff overtime. The Commission has provided guidance concerning the application of standards of no significant hazards consideration determination by providing certain examples (April 6, 1983, 48 FR 14870). One of the examples of actions likely to involve no significant hazards consideration [example (ii)] relates to a change that constitutes an additional limitation, restriction, or control not presently included in the Technical Specifications: for example, a more stringent surveillance requirement. Since staff overtime limits are not addressed in the current Technical Specifications, the proposed change falls within the category of example (ii). Therefore, the staff proposes to determine that the requested action would involve a no significant hazards consideration determination in that it (1) does not involve a significant increase in the probability or consequences of a previously evaluated accident; (2) does not create the possibility of a new or different kind of accident from an accident previously evaluated; and (3) does not involve a significant reduction in a margin of safety.

Local Public Document Room location: San Clemente Public Library, 242 Avenida Del Mar, San Clemente, California 92672.

Attorney for licensee: Charles R. Kocher, Assistant General Counsel, James Beoletto, Esquire, Southern California Edison Company, Post Office Box 800, Rosemead, California 91770.

NRC Branch Chief: John A. Zwolinski.

Tennessee Valley Authority, Docket Nos. 50–259, 50–260 and 50–296, Browns Ferry Nuclear Plant, Units 1, 2 and 3, Limestone County, Alabama

Date of amendment request: October 22, 1984.

Description of amendment request: The amendments would modify the Technical Specifications (TS) to:

1. Provide Limiting Conditions for Operation and Surveillance Requirements as necessary to permit the 161KV Trinity power transmission line and both common station service transformers to serve as an offsite power source to two operating units, and the 161KV Athens line and one common station service transformer to serve as an offsite power source to one operating unit, subject to the condition that the 161KV system is not used as a required offsite power source for more than two operating units. A cooling tower transformer could be substituted for a common station service transformer when no cooling tower pumps or fans are running.

2. Revise the setpoints and setpoint tolerance limits for Units 1 and 2 4KV shutdown board undervoltage relay timers. The setpoints and tolerance limits will be revised to reflect values achievable with pneumatic relays.

3. Revise text to more clearly identify acceptable offsite power source selections.

4. Revise text to more clearly identify 480VAC switchboard requirements. The boards will be identified individually rather than generically (i.e., change "480–V RMOV boards D and E" to "480–V boards 1D and 1E"). This will reduce confusion regarding shared equipment.

5. Remove the requirement to record weekly the temperature of the cells adjacent to the pilot cells of the unit batteries, diesel generator batteries, and shutdown board batteries, and replace it with a requirement to record the temperature of the pilot cells weekly.

6. Reword a surveillance requirement relating to automatic load sequencing to clarify that there is no load sequencer. (Load sequencing is accomplished by timers and relays.)

Basis for proposed no significant hazards consideration determination: The Commission has provided guidance for the application of criteria for no significant hazards consideration determination by providing examples of amendments that are considered not likely to involve significant hazards considerations (48 FR 14870). These examples include: "(i) A purely administrative change to Technical Specifications: For example, a change to achieve consistency throughout the Technical Specifications, correction of an error, or a change in nomenclature. (ii) A change that constitutes an additional limitation, restriction, or control not presently included in the Technical Specifications: For example, a more stringent surveillance requirement. (vi) A change which either may result in some increase to the probability or consequences of a previously-analyzed accident or reduce in some way a safety margin, but where the results of the change are clearly within all acceptable criteria with respect to the system or component specified in the Standard Review Plan (SRP): For example, a change resulting from the application of a small refinement of a previously used calculational model or design method."

Change 1 may result in higher loads on certain components of the offsite power system and may thus affect the probability of loss of offsite power. This may in turn affect the probability or consequences of a previously-analyzed accident. However, the Athens and Trinity 161KV systems each meet the

SRP Chapter 8.2 acceptance criteria for an offsite power source and would thus be acceptably reliable. The proposed change is consistent with the acceptance criteria of SRP Chapter 8.2 and is encompassed by example (vi).

Change 2 involves more restrictive (conservative) requirements for certain Units 1 and 2 undervoltage relays, and less restrictive requirements for others. The former are encompassed by example (ii). For the latter, the revised setpoints and tolerance limits may result in some additional delay in protective actions. However, the revised requirements assure that the relay operating times will be less than the critical values stated in the TS. These changes conform to the acceptance criteria of Chapter 8.3.2 of the SRP and are therefor encompassed by example (vi).

Changes 3, 4 and 6 neither add, delete nor modify any requirements. The revised wording and nomenclature serves only to provide clarification of existing requirements. They are therefore administrative changes encompassed by example (i).

Change 5 modifies surveillance requirements for batteries and therefore may possibly increase the probability of loss of DC power. This may in turn affect the probability or consequences of a previously-analyzed accident. However, the revised requirements would be consistent with NUREG–0123, the Standard Technical Specifications (STS). The STS specify weekly surveillance of the pilot cell only. Since the STS serve as the basis for assessing conformance to the SRP Chapter 16 and the change is consistent with the STS, Change 5 is encompassed by example (vi).

Since the application for amendment involves proposed changes that are encompassed by an example for which no significant hazards consideration exists, the staff has made a proposed determination that the application involves no significant hazards consideration.

Local Public Document Room location: Athens Public Library, South and Forrest, Athens, Alabama 35611.

Attorney for licensee: H.S. Sanger, Jr., Esquire, General Counsel, Tennessee Valley Authority, 400 Commerce Avenue, E 11B 33C, Knoxville, Tennessee 37902.

NRC Branch Chief: Domenic B. Vassalo.

Union Electric Company, Docket 50–483, Callaway Plan, Unit No. 1, Callaway County, Missouri

Date of amendment request: December 28, 1984.

Description of amendment request: The purpose of the proposed amendment request is to revise License Condition 2.C.(3).(a) of Facility Operating License NPF–30 to incorporate a November 30, 1985 deadline for the environmental qualification of all safety-related electrical equipment. Section 50.49(i) of the Commission's Regulations, which is applicable to the Callaway Plant, does not appear to require the March 31, 1985 deadline currently in the license. The Callaway licensee has previously submitted Justification for Interim Operation (JIO's) which have addressed the requirements of 10 CFR 50.49(i) and will remain valid through November 30, 1985. The discussions in these JIO's ensure that the plant can be safely operated pending completion of equipment qualification. The staff has concluded that Union Electric Company has demonstrated conformance with the qualification requirements of 10 CFR 50.49 (Supplement 3 to Callaway Safety Evaluation Report, NUREG–0830, Section 3.11.5).

Precedents have been set regarding recently issued operating licenses that included November 30, 1985 qualification deadlines. In particular, Facility Operating License NPF–23 for Byron Station, Unit 1, issued subsequent to NPF–25 (Callaway low-power license), has a November 30, 1985 environmental qualification deadline. It is noted that the outstanding Westinghouse qualification programs are generic to Callaway and Byron.

Basis for proposed no significant hazards consideration determination: The licensee, in his letter of December 28, 1984, stated that the proposed change does not involve a significant increase in the probability or consequences of an accident or other adverse condition over previous evaluations; nor create the possibility of a new or different kind of accident or condition over previous evaluations; nor involve a significant reduction in a margin of safety. Based on the foregoing, the requested amendment does not present a significant hazard. The Commission has provided guidance concerning the application of the Standards in 10 CFR 50.92 by providing certain examples (48 FR 14870). This amendment request is similar to the example of an action involving no significant hazards consideration which relates to a change to make the license conform to regulations, where the license amendment results in very minor changes to facility operations clearly in keeping with the regulations. The staff has made a significant hazards determination and has concluded that this amendment request does not result in a significant hazards consideration because previously submitted JIO's which have addressed the requirements of 10 CFR 50.49(i) will remain valid through November 30, 1985. The discussions in these JIO's ensure that the plant can be safely operated pending completion of equipment qualification.

Local Public Document Room locations: Fulton City Library, 709 Market Street, Fulton, Missouri 65251 and the Olin Library of Washington University, Skinker and Lindell Boulevards, St. Louis, Missouri, 63130.

Attorney for licensee: Gerald Charnoff, Esq., Shaw, Pittman, Potts & Trowbridge, 1800 M Street, NW., Washington, D.C. 20036.

NRC Branch Chief: B.J. Youngblood.

Vermont Yankee Nuclear Power Corporation, Docket No. 50–271, Vermont Yankee Nuclear Power Station, Vernon, Vermont

Date of application for amendment: February 7, 1983, as supplemented October 22, 1984 and November 6, 1984.

Description of amendment request: This submittal supplements the request for amendment dated February 7, 1983 which was noticed in the **Federal Register** on April 25, 1984 (49 FR 17876). This supplements the request for amendment dated February 7, 1983 which was noticed in the **Federal Register** on April 25, 1984 (49 FR 17876). This supplemental request for Technical Specification (TS) change relates to the operability and testing requirements for hydraulic shock suppressors (snubbers).

The proposed changes were made in response to an NRC request to upgrade the testing requirements for all safety-related snubbers to ensure a higher degree of operability. The changes involve: Clarifying the frequency for visual inspection, stating the requirements for functional testing of snubbers which visually appear inoperable, the inclusion of a formula for the selection of representative sample sizes, and the clarifying of the testing acceptance criteria.

Basis for proposed no significant hazards consideration determination: The Commission has provided guidance concerning the application of these standards by providing certain examples (48 FR 14870). The examples of actions involving no significant hazards considerations include changes that constitute additional limitations or restrictions in the Technical Specifications. The proposed changes revise sections of the Technical Specifications related to hydraulic snubbers to clarify requirements and to

incorporate both operability and testing requirements. Since the requested changes upgrade the requirements for hydraulic snubbers, the staff proposes to determine that the application does not involve a significant hazards consideration, since the change is similar to the above example.

Local Public Document Room location: Brooks Memorial library, 224 Main Street, Brattleboro, Vermont 05301.

Attorney for licensee: John A. Ritscher, Esquire, Ropes and Gray, 225 Franklin Street, Boston, Massachusetts 02110.

NRC Branch Chief: Domenic B. Vassallo.

Wisconsin Electric Power Company, Docket No. 50–266, Point Beach Nuclear Plant, Unit No. 1, Town of Two Creeks, Manitowoc County, Wisconsin

Date of amendment request: November 9, 1984 as modified November 14, 1984.

Description of amendment request: The application proposes changes to the Technical Specifications for Point Beach Unit No. 1. Specifically, the overtemperature and overpower delta T equations of Technical Specifications 15.2.3.1.B(4) and 15.2.3.1.B(5), respectively, would be modified to specify additional time constraints utilized in the measured delta T and average temperature lag compensations which are part of the instrumentation for the overpressure and overpower delta T circuitry.

Basis for proposed no significant hazards consideration determination: The licensee's proposed changes to the Technical Specifications for the overtemperature and overpower delta T equations are identical to those requested and recently issued for Point Beach Unit 2. The changes are needed because of the licensee's plans to use Westinghouse Optimized Fuel Assemblies during the next Unit 1 refueling outage. Sostman resistance temperature detectors (RTDs) previously installed in Unit 2 and presently installed in Unit 1 are unable to be accurately calibrated in accordance with new calibration procedures resulting from the licensee's use of Westinghouse Optimized Fuel Assemblies. The licensee determined that replacing Sostman RTDs with Rosemont RTDs, which are widely used in the industry, would satisfy the calibration difficulties. Westinghouse recommended that a two-second time-delay filter be used in conjunction with the Rosemont RTDs to minimize the potential for spurious reactor trips and runbacks.

The time delay associated with the Sostman RTDs is approximately equal to the combined time delay of the Rosemont RTDs plus the two-second time-delay filter. The filter had always been a part of the original design circuitry but was never analyzed because of the sufficient time delay associated with the Sostman RTDs. Using the filter in conjunction with the new Rosemont RTD time constant has necessitated that modifications be made to the overpower and overtemperature delta T equations to reflect the additional time constants in the equations.

From an analytical and electrical point of view, there is negligible difference between use of a Sostman RTD with no filter or a Rosemont RTD with a two-second filter. Indeed, the change to the overtemperature delta T and overower delta T equations requested in this application does no more than add a mathematical term (1/1+t) which was always implicit in the equations in the existing Technical Specifications, but was never explicitly stated because, with the Sostman RTDs incorporating a built-in filter, t was equal to 0 and 1/1+0 was equal to 1. Further, the licensee's proposed Technical Specifications conform to the overpower and overtemperature delta T equations of the Standard Technical Specifications.

Since the requested operational mode, plant operating conditions, the physical status of the plant, system response, and dose consequences of potential accidents are the same as without the requested change, the staff concludes that:

(1) Operation of the facility in accordance with the amendment would not significantly increase the probability or consequences of an accident previously evaluated.

(2) Operation of the facility in accordance with the amendment would not create the possibility of a new or different kind of accident from any accident previously evaluated.

(3) Operation of the facility in accordance with the amendment would not involve a significant reduction in a margin of safety.

Based on the above, the staff proposes to determine the proposed amendment involves no significant hazards consideration.

Local Public Document Room location: Joseph P. Mann Public Library, 1516 Sixteenth Street, Two Rivers, Wisconsin.

Attorney for licensee: Gerald Charnoff, Esq., Shaw, Pittman, Potts & Trowbridge, 1800 M Street NW., Washington, D.C. 20036.

NRC Branch Chief: James R. Miller.

Wisconsin Electric Power Company, Docket Nos. 50–266 and 50–301, Point Beach Nuclear Plant, Unit Nos. 1 and 2, Town of Two Creeks, Manitowoc County, Wisconsin

Date of amendment request: September 26, 1984.

Description of amendment request: The application modifies an earlier amendment request dated March 16, 1984. A proposed no significant hazards consideration determination was made by the staff and notice was published in the **Federal Register** on June 20, 1984 (49 FR 25350 at 25381).

This application modifies the previous application by deleting shock suppressors (snubbers), Table 15.3.13–1, and references thereto in specifications in accordance with NRC Generic Letter 84–13, " Technical Specification for Snubbers", dated May 3, 1984. Additionally, Specification 15.4.13.2 has been changed to require the functional testing of a representative sample of approximately 10 percent of the safety-related snubbers. This change more accurately reflects the intent of the requirement of functional testing and makes the specfication independent of the number of safety-related snubbers.

This specification also incorporates recent organizational changes for senior management of Wisconsin Electric Power Company. Specifications 15.6.5.1, "Manager's Supervisory Staff", 15.6.5.3, "Off-site Review Committee", 15.6.6, "Reportable Occurrence Action", and 15.6.7, "Action to be Taken if a Safety Limit is Exceeded", and Figures 15.6.2–1 and 15.6.2–3 have been changed to reflect the creation of the position of Vice Chairman of the Board and elimination of the position of Executive Vice President. The application also corrects various typographical and clerical errors in the previous submittal and makes minor clarifying change such as that designation of the Duty and Call Superintendent by the Manager shall be in writing.

Basis for proposed no significant hazards consideration determination: The Commission has provided guidance concerning the application of these standards by providing certain examples (48 FR 14870). One of the examples of actions likely to involve no significant hazards considerations is a purely administrative change to technical specifications: For example, a change to achieve consistency throughout the technical specifications, correction of an error or a change in nomenclature. The changes in organizational titles, correction of

typographical and clerical errors and minor clarifying changes are of this type.

The changes related to safety related snubbers limiting conditions for operation and surveillance requirements follow the staff guidance contained in Generic Letter 84–13 dated May 3, 1984. The list of safety related snubbers has been deleted from the Technical Specifications. The provision that all safety related snubbers shall be subject to the limiting conditions for operation and surveillance requirements has been substituted in its place. The requirements have not changed other than to change the actual number of snubbers surveilled per interval to the percentage of the overall number of safety related snubbers. This would clarify the need for increasing the surveillance size should the licensee add new snubbers to the plant.

Deleting the listing of safety related snubbers from the Technical Specifications will not affect the operability and surveillance requirements of these snubbers. They will still be required to meet the limiting conditions for operation of the units. Therefore, the changes do not involve a significant increase in the probability or consequences of an accident previously evaluated. Nor do they create the possibility of a new or different kind of accident from any accident previously evaluated. Because all of the limiting conditions for operation and the surveillance requirements remain essentially the same except for minor clarifications, the amendment do not involve a significant reduction in a margin of safety. Based on the original amendment application involve no significant hazards considerations.

Local Public Document Room location: Joseph P. Mann Public Library, 1516 Sixteenth Street, Two Rivers, Wisconsin.

Attorney for licensee: Gerald Charnoff, Esq., Shaw, Pittman, Potts & Trowbridge, 1800 M Street NW., Washington, D.C. 20036.

NRC Branch Chief: James R. Miller.

PREVIOUSLY PUBLISHED NOTICES OF CONSIDERATION OF ISSUANCE OF AMENDMENTS TO OPERATING LICENSES AND PROPOSED NO SIGNIFICANT HAZARDS CONSIDERATION DETERMINATION AND OPPORTUNITY FOR HEARING

The following notices were previously published as separate individual notices. The notice content was the same as above. They were published as individual notices because time did not allow the Commission to wait for this regular monthly notice. They are repeated here because the monthly notice lists all amendments proposed to be issued involving no significant hazards consideration.

For details, see the individual notice in the **Federal Register** on the day and page cited. This notice does not extend the notice period of the original notice.

Pennsylvania Power & Light Company, Docket No. 50–387, 50–388 Susquehanna Steam Electric Station (SSES), Units 1 & 2 Luzerne County, Pennsylvania

Date of amendment request: December 6, 1984.

Description of amendment request: The purpose of the proposed changes to the SSES Unit 1 and Unit 2 technical specifications is to avoid a forced shutdown of Unit 2 during the Unit 1 refueling outage. Presently, SSES Unit 2 currently depends on certain SSES Unit 1 125-volt batteries to support loads common to both units. As a result, Unit 1 batteries are listed in Unit 2 Limiting Conditions for Operating (LCOs) on the DC system. As the Unit 1 and Unit 2 Technical Specifications are now written whenever the Unit 1 125-volt batteries are unavailable Unit 1 and Unit 2 must shutdown after a short time period if the 125-volt power sources are not restored.

During the Unit 1 refueling outage (presently scheduled for February 1985) the Unit 1 batteries must undergo battery load profile testing. The battery tests are scheduled to be performed within the first week of the refueling outage. This battery load profile testing results in the unavailability of Unit 1 125-volt batteries forcing Unit 2 to shutdown during the aforementioned testing. The licensee is proposing to modify the 125-volt DC system in order to provide an alternative means of supplying common loads. This proposal includes providing a common load transfer scheme which will allow common loads to be powered from a 125-volt DC source on either unit through the use manual transfer switches. It should be noted that during normal operations of Unit 1 and 2 this proposed amendment only allows Unit 2 to remain operating upon loss of the Unit 1 125-volt DC power source. Provisions have been made in the proposed technical specification changes to provide for implementation of the common load transfer. Plant modifications will provide the hardware capability to feed the common loads from the Unit 1 and Unit 2 DC sources.

The Unit 1 Technical Specification changes reflect the addition of several action statements to instruct the operator to transfer common loads to the Unit 2 DC source upon loss of Unit 1 DC source. Additionally Unit 1 technical specifications make provision for the loss of the Unit 2 DC source subsequent to the loss of Unit 1 DC source. The Unit 2 Technical Specification changes reflect the addition of action statements to instruct the operator to transfer loads back to the Unit 1 DC source when the Unit 1 DC source is again operable. Provisions have also been made in the Unit 2 technical specifications for the loss of Unit 2 DC source when supporting common loads. The changes proposed allow increased operational flexibility in addition to adding a redundant feature, being the alternative means of providing 125-volt DC power source.

Date of publication of individual notice in **Federal Register:** January 7, 1985 (50 FR 904).

Expiration date of individual notice: February 7, 1985.

Local Public Document Room Location: Osterhout Free Library, Reference Department, 71 South Franklin Street, Wilkes-Barre, Pennsylvania 18701.

Power Authority of the State of New York, Docket No. 50–333, James A. FitzPatrick Nuclear Power Plant, Oswego County, New York

Date of amendment request: October 2, 1984, as supplemented October 22, 1984.

Brief description of amendment: These revisions would permit higher settings in normal full power background trip level setting for the main Steam Line High Radiation scram and isolation setpoints to accommodate a scheduled short-term test. This test would examine the potential of hydrogen addition to the feedwater as a means of mitigating stress corrosion cracking.

Date of publication of individual notice in **Federal Register:** December 14, 1984 49 FR 48842.

Expiration date of individual notice: January 14, 1985.

Local Public Document Room location: Penfield Library, State University College at Oswego, Oswego, New York.

Sacramento Municipal Utility District, Docket No. 50–312, Rancho Seco Nuclear Generating Station, Sacramento County, California

Date of amendment request: October 16, 1984, revised November 8, 1984.

Brief description of amendment: The amendment would revise the Technical Specifications to allow on a one time only basis, the extension of the definition of refueling interval from 18 months to two months beyond the

maximum 25% extension for performance of the refueling interval surveillance test of the Reactor Internal Vent Valves. The temporary definition of the refueling interval for the reactor Internal Vent Valves will expire on startup from the 1985 refueling outage.

Date of publication of individual notice in **Federal Register:** December 20, 1984, 49 FR 49528.

Expiration date of individual notice: January 22, 1985.

Local Public Document Room location: Sacramento City-County Library, 828 I Street, Sacramento, California.

NOTICE OF ISSUANCE OF AMENDMENT TO FACILITY OPERATING LICENSE

During the 30-day period since publication of the last monthly notice, the Commission has issued the following amendments. The Commission has determined for each of these amendments that the application complies with the standards and requirements of the Atomic Energy Act of 1954, as amened (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Chapter I, which are set forth in the license amendment.

Notice of Consideration of Issurance of Amendment to Facility Operating License and Proposed No Significant Hazards Consideration Determination and Opportunity for Hearing in connection with these actions was published in the **Federal Register** as indicated. No request for a hearing or petition for leave to intervene was filed following this notice.

Unless otherwise indicated, the Commission has determined that these amendments satisfy the criteria for categorical exclusion in accordance with 10 CFR 51.22. Therefore, pursuant to 10 CFR 51.22(b), no environmental impact statement or environmental assessment need be prepared for these amendments. If the Commission has prepared an environmental assessment under the special circumstances provision in 10 CFR 51.12(b) and has made a determination based on that assessment, it is so indicated.

For further details with respect to the action see (1) the applications for amendments, (2) the amendments, and (3) the Commission's related letters, Safety Evaluations and/or Environmental Assessments as indicated. All of these items are available for public inspection at the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C., and at the local public document rooms for the particular facilities involved. A copy of items (2) and (3) may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Licensing.

Alabama Power Company, Docket Nos. 50–348 and 50–364, Joseph M. Farley Nuclear Plant, Unit Nos. 1 and 2, Houston County, Alabama

Date for application for amendments: July 6, 1984.

Brief description of amendments: Technical Specifications are modified to remove the listings of snubbers (Table 3.7–4a) in accordance with Commission direction of Generic Letter 84–13. Other administrative changes and typographical corrections are also made.

Date of issuance: December 19, 1984.

Effective date: December 19, 1984.

Amendment Nos.: 55 and 46.

Facilities Operating License Nos. NFP–2 and NPF–8. Amendments revised the Technical Specifications.

Date of initial notice in **Federal Register:** August 22, 1984 (49 FR 33354).

The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 19, 1984.

No siginficant hazards consideration comments were received.

Local Public Document Room location: George S. Houston Memorial Library, 212 W. Burdeshaw Street, Dothan, Alabama 36303.

Alabama Power Company, Docket Nos. 50–348 and 50–364, Joseph M. Farley Nuclear Plant, Unit Nos. 1 and 2, Houston County, Alabama

Date for application for amendments: November 2, 1984.

Brief description of amendments: Technical Specifications, Administrative Controls Section 6, is revised to delete "8-hour work day" but to maintain the nominal 40-hour work week.

Date of issuance: December 26, 1984.

Effective date: December 26, 1984.

Amendment Nos.: 56 and 47.

Facilities Operating License Nos. NFP–2 and NPF–8. Amendments revised the Technical Specifications.

Date of initial notice in **Federal Register:** November 21, 1984 (49 FR 45942).

The Commission's related evaluation of the amendment is contained in a Safety Evaulation dated December 26, 1984.

No significant hazards consideration comments were received.

Local Public Document Room location: George S. Houston Memorial Library, 212 W. Burdeshaw Street, Dothan, Alabama 36303.

Arkansas Power and Light Company, Docket No. 50–313, Arkansas Nuclear One, Unit No. 1, Pope County, Arkansas.

Date of application for amendment: October 15, 1985.

Brief description of amendment: The amendment reflects, in the Technical Specifications, the actual number of instrument channels for the detection of pressurizer level, which will be available following modifications to upgrade these instruments during the sixth refueling outage.

Date of issuance: December 20, 1984.

Effective date: December 20, 1984.

Amendment No: 89.

Facility Operating License No. DPR–51. Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** November 19, 1984 (49 FR 45677).

The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 20, 1984.

No significant hazards consideration comments received: No.

Local Public Document Room location: Tomlinson Library, Arkansas Tech University, Russellville, Arkansas 72801.

Arkansas Power and Light Company, Docket No. 50–313, Arkansas Nuclear One, Unit No. 1, Pope County, Arkansas.

Date of application for amendment: October 9, 1984.

Brief description of amendment: The amendment revises the TSs to allow the ten-year hydrostatic test of the secondary system to be performed using steam in lieu of water.

Date of issuance: December 20, 1984.

Effective date: December 20, 1984.

Amendment No: 90.

Facility Operating License No. DPR–51. Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** November 19, 1984 (49 FR 45680).

The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 20, 1984.

No significant hazards consideration comments received: No.

Local Public Document Room location: Tomlinson Library, Arkansas Tech University, Russellville, Arkansas 72801.

Arkansas Power and Light Company, Docket No. 50–313, Arkansas Nuclear One, Unit No. 1, Pope County, Arkansas

Date of application for amendment: September 12, 1984, as supplemented November 8, 1984.

Brief description of amendment: The amendment revises the TSs by providing operating requirements, limiting conditions for operation, and surveillance requirements for the upgrades in the Emergency Feedwater System and reflects the deletion of the Steam Line Break Instrumentation and Control System.

Date of issuance: December 20, 1984.

Effective date: December 20, 1984.

Amendment No: 91.

Facility Operating License No. DPR–51. Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** November 19, 1984 (49 FR 45676).

The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 20, 1984.

No significant hazards consideration comments received: No.

Local Public Document Room location: Tomlinson Library, Arkansas Tech University, Russellville, Arkansas 72801.

Arkansas Power and Light Company, Docket No. 50–313, Arkansas Nuclear One, Unit No. 1, Pope County, Arkansas

Date of application for amendment: September 26, 1984, as supplemented October 31, 1984.

Brief description of amendment: The amendment revises the TSs to support the operation of ANO–1 at full rated power during the Cycle 7.

Date of issuance: December 20, 1984.

Effective date: December 20, 1984.

Amendment No: 92.

Facility Operating License No. DPR–51. Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** November 19, 1984 (49 FR 45679).

The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 20, 1984.

No significant hazards consideration comments received: No.

Local Public Document Room location: Tomlinson Library, Arkansas Tech University, Russellville, Arkansas 72801.

Arkansas Power and Light Company, Docket Nos. 50–313 and 50–368, Arkansas Nuclear One, Unit 1 and Unit 2, Pope County, Arkansas

Date of application for amendment: October 31, 1980 as supplemented and revised August 23, 1983 and July 11, 1984.

Brief description of amendment: The amendments revised the Technical Specifications (TS) to incorporate hdrogen/oxygen concentration limitations and hydrogen/oxygen monitoring requirements in the ANO 1 & 2 radioactive waste gas systems.

Date of issuance: January 14, 1985.

Effective date: January 14, 1985.

Amendment Nos.: 93 and 61.

Facility Operating License Nos. DPR–51 and NPF–6. Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** August 23, 1983, 48 FR 38387; November 22, 1983, 48 FR 52805; and September 28, 1984, 49 FR 38393.

The Commission's related evaluation of the amendments is contained in a Safety Evaluation dated January 14, 1985.

No significant hazards consideration comments received. No

Local Public Doucment Room location: Tomlinson Library, Arkansas Tech University, Russellville, Arkansas 72801.

Baltimore Gas & Electric Company, Docket Nos. 50–317 and 50–318, Calvert Cliffs Nuclear Power Plant, Unit Nos. 1 and 2, Calvert County, Maryland

Date of application for amendments: April 9, 1984 and June 29, 1984.

Brief description of amendments: The amendments changed the Unit 1 and Unit 2 Technical Specifications (TS) to reflect: (1) A change to the surveillance requirements for fire pumps to allow an alternate test method, (2) correction of a typographical error in a Unit 1 fire pump surveillance test, (3) clarification and correction of a typographical error concerning fire hose stations, (4) clarification of operability requirements for the component cooling water system, (5) clarification of valve surveillance for component cooling, service water and salt water systems, and (6) provisions for backup instrumentation for the remote shutdown, wide range neutron flux instrumentation.

These changes to the TS are in partial response to the applications dated April 9, 1984 and June 29, 1984. The remaining issues addressed in these applications will be addressed in future correspondence.

Date of issuance: January 14, 1985.

Effective date: January 14, 1985.

Amendment Nos.: 97 and 79.

Facility Operating License Nos. DPR–53 and DPR–69: Amendments revised the Technical Specifications.

Date of initial notice in **Federal Register:** September 28, 1984 (49 FR 38390 at 38393).

The Commission's related evaluation of the amendments is contained in a Safety Evaluation dated January 14, 1985.

No significant hazards consideration comments received: No.

Local Public Document Room location: Calvert County Library, Prince Frederick, Maryland.

Carolina Power and Light Company, Docket No. 50–261, H. B. Robinson Steam Electric Plant, Unit No. 2, Darlington, South Carolina

Date of application for amendment: May 7, 1984.

Brief description of amendment: The amendment revises the Appendix A Technical Specifications to add a limiting condition for operation and basis for backfeeding safety related busses through the main and unit auxiliary transformers.

Date of issuance: January 2, 1985.

Effective date: January 2, 1985.

Amendment No. 88.

Facility Operating License No. DPR–23: Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** August 22, 1984 (49 FR 33361) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated January 2, 1985.

Significant hazards consideration comments received: No.

Local Public Document Room location: Hartsville Memorial Library, Home and Fifth Avenues, Hartsville, South Carolina 29535.

Commonwealth Edison Company, Docket Nos. 50–373 and 50–374, La Salle County Station, Units 1 and 2, La Salle County, Illinois

Date of application for amendment: These amendments change the La Salle Unit 1 and Unit 2 Technical Specifications consistent with a design change in the location of the reactor water cleanup (RWCU) pumps to a point in the system containing lower temperature water. The Technical Specifications change eliminates the requirement to specify limits on the ambient and differential temperature measrement in the RWCU pump rooms in Tables 3.3.2–1, 3.3.2–2, 3.3.2–3, and 4.3.2.1–1 because the ambient and differential temperature trip setpoints for these temperature channels (set at

temperatures for equivalent leakage) are very near normal operating temperatures. This has caused spurious isolation (no leaks present). Because of the change in the location of these pumps, these temperature channels and their logic trip inputs are unnecessary. Sufficient diversity remains to ensure that RWCU leakage in the pump rooms is monitored and promptly will be isolated.

Date of issuance: January 8, 1985.
Effective date: January 8, 1985.
Amendment Nos: 20 and 7.
Facility Operating Licenses No. NPF-11 and NPR-18: Amendment revised the Technical Specifications
Date of initial notice in **Federal Register:** November 21, 1984 (49 FR 45946). The Commission's related evaluation of the amendments is contained in a Safety Evaluation dated January 8, 1985.

No significant hazards consideration comments received: None.

Local Public Document Room location: Public Library of Illinois Valley Community College, Rural Route No. 1, Ogelsby, Illinois 61348.

Consolidated Edison Company of New York, Docket Nos. 50-3 and 50-247, Indian Point Nuclear Generating Unit Nos. 1 and 2, Westchester County, New York

Date of application for amendments: September 29, 1983.

Brief description of amendment: The amendments revise Figures 3.1 and 3.2 of the Indian Point Unit No. 1 Technical Specifications and Figures 6.2.1 and 6.2.2 of the Indian Point Unit No. 2 Technical Specifications thereby consolidating the fire protection responsibilities of the Fire Protection and Safety Administration with those of the Fire and Property Protection Engineer. The amendment also changes the number of copies of the monthly operating report sent to the Office of Inspection and Enforcement and deletes the requirement to send the report to the Office of Management Information and Control.

Date of issuance: January 10, 1985.
Effective date: January 10, 1985.
Amendment Nos: 33 and 92.
Facilities Operating License No. DPR-26: Amendment revised the Technical Specifications.
Date of initial notice in **Federal Register:** April 25, 1984 (49 FR 17857). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated January 10, 1985.

Significant hazards consideration comments received: No.

Local Public Document Room location: White Plains Public Library, 100 Martine Avenue, White Plains, New York, 10610.

Consolidated Edison Company of New York, Docket No. 50-247, Indian Point Nuclear Generating Unit No. 2, Westchester County, New York

Date of application for amendment: February 14, 1983, as supplemented June 29, 1984.

Brief description of amendment: The amendment to the Technical Specifications modifies the definition of the term "Operable" as it applies to a single-failure criterion for safety systems. Certain editorial and format changes were also made.

The modification to the term operable was initially proposed by a February 14, 1983 license amendment application. This definition of operable alone was not consistent with the required definition contained in NRC's April 10, 1980 generic letter. However, supplemental modifications contained in a June 29, 1984 licensee amendment application provided a definition consistent with NRC requirements. The original license amendment application dated February 14, 1983 was not specifically noticed in the **Federal Register.** However, acceptable notice was accomplished through noticing of the June 29, 1984 application which referenced the February 14 application repeatedly.

Date of issuance: December 26, 1984.
Effective date: December 26, 1984.
Amendment No.: 91.
Facilities Operating License No. DPR-26: Amendment revised the Technical Specifications.
Date of initial notice in **Federal Register:** September 28, 1984 (49 FR 38396).

The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 26, 1984.

Significant hazards consideration comments received: No.

Lcoal Public Document Room location: White Plains Public Library, 100 Martine Avenue, White Plains, New York 10610.

Dairyland Power Cooperative, Docket No. 50-409, La Crosse Boiling Water Reactor, Vernon County, Wisconsin

Date of application for amendment: April 4, 1983 and August 23, 1984.

Brief description of amendment: The amendment modifies the Appendix A Technical Specifications by adding requirements which restrict overtime of certain plant personnel and require reporting of all indicated operations of primary system safety valves for pressure relief purposes.

Date of Issuance: January 8, 1985.
Effective date: January 8, 1985.
Amendment No.: 38.
Provisional Operating License No. DPR-45. Amendment revised the Appendix A Technical Specifications.
Date of initial notice in **Federal Register:** August 23, 1983 (48 FR 38400) and October 24, 1984 (49 FR 42816).

The Commission's related evaluation for the license amendment is contained in a Safety Evaluation dated January 8, 1984.

No significant hazards consideration comments received: No.

Local-Public Document Room location: La Crosse Public Library, 800 Main Street, La Crosse, Wisconsin 54601.

Duquesne Light Company, Docket No. 50-334, Beaver Valley Power Station, Unit No. 1, Shippingport, Pennsylvania

Date of application for amendment: July 14, 1983.

Brief description of amendment: The amendment changes the Technical Specifications for Beaver Valley Unit No. 1 to allow air lock leak tests be performed only upon completion of maintenance that could affect the air lock sealing capability. This amendment involves an exemption to Section III.D.2(b)(ii) of Appendix J of 10 CFR Part 50; the exemption was granted on November 19, 1984. Also, Amendment Nos. 75, 82 and 83 have been issued on all other issues addressed by this request.

Date of issuance: November 19, 1984.
Effective date: November 19, 1984.
Amendment No.: 85.
Facility Operating License No. DPR-66. Amendment revised the Technical Specifications.
Date of initial notice in **Federal Register:** October 26, 1983 (48 FR 49585). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated November 19, 1984.

No significant hazards consideration comments received: None.

Local Public Document Room location: B. F. Jones Memorial Library, 663 Franklin Avenue, Aliquippa, Pennsylvania 15001.

Duquesne Light Company, Docket No. 50-334, Beaver Valley Power Station, Unit No. 1, Shippingport, Pennsylvania

Date of application for amendment: May 21, 1984.

Brief description of amendment: The amendment changes the Technical Specifications for Beaver Valley Unit No. 1 to reflect the revised capsule removal schedule recommended by Westinghouse Topical Report WCAP-

9860. The Bases have also been revised to reference 10 CFR Part 50 Appendix H for capsule removal and evaluation. The changes would bring the surveillance schedule into conformance with Appendix H, "Reactor Vessel Material Surveillance Program Requirements" of 10 CFR Part 50.

Date of issuance: November 19, 1984.
Effective date: November 19, 1984.
Amendment No.: 86.
Facility Operating License No. DPR–66: Amendment revised the Technical Specifications.
Date of initial notice in Federal Register: July 24, 1984 (49 FR 29907). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated November 19, 1984.
No significant hazards consideration comments received: None.
Local Public Document Room location: B. F. Jones Memorial Library, 663 Franklin Avenue, Aliquippa, Pennsylvania 15001.

Duquesne Light Company, Docket No. 50–334, Beaver Valley Power Station, Unit No. 1, Shippingport, Pennsylvania

Date of application for amendment: June 25, 1984
Brief description of amendment: The amendment changes the Technical Specifications for Beaver Valley Unit No. 1 to detach the schedule for the containment Type A leak test from the schedule of inservice inspection. An exemption from 10 CFR Part 50, Appendix J, Section III.D.1(a), was granted on December 5, 1984, allowing that this amendment be issued. The new technical specification still requires that Type A leak tests be done at 40± 10-month intervals even though they no longer need to be performed in conjunction with inservice inspection.
Date of issuance: December 31, 1984.
Effective date: December 31, 1984.
Amendment No: 87.
Facility Operating License No. DPR–66. Amendment revised the Technical Specifications.
Date of initial notice in Federal Register: August 22, 1984 (49 FR 33363). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 31, 1984.
No significant hazards consideration comments received: None.
Local Public Document Room location: B. F. Jones Memorial Library, 663 Franklin Avenue, Aliquippa, Pennsylvania 15001.

Duquesne Light Company, Docket No. 50–334, Beaver Valley Power Station, Unit No. 1, Shippingport, Pennsylvania

Date of application for amendment: September 5, 1984.
Brief description of amendment: The amendment changes the Technical Specifications for Beaver Valley Unit No. 1 to conform with guidance provided in the Standard Technical Specifications as follows: (1) The requirement to inspect in-containment areas where fire detection instruments have become inoperable has been changed from once per hour to once per 8 hours, or to monitor containment air temperature at selected locations once per hour. (2) The requirement to perform channel functional test on fire detection instruments not accessible during plant operation has been changed from once every 6 months to "during cold shutdown exceeding 24 hours." (3) The reporting requirement for inoperable fire detection instrument has been changed to comply with 10 CFR 50.72 and 50.73.
Date of issuance: December 31, 1984.
Effective date: December 31, 1984.
Amendment No: 88.
Facility Operating License No. DPR–66: Amendment revised the Technical Specifications.
Date of initial notice in Federal Register: October 24, 1984 (49 FR 42818). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 31, 1984.
No significant hazards consideration comments received: None.
Local Public Document Room location: B. F. Jones Memorial Library, 663 Franklin Avenue, Aliquippa, Pennsylvania 15001.

Duquesne Light Company, Docket No. 50–334, Beaver Valley Power Station, Unit No. 1, Shippingport, Pennsylvania

Date of application for amendment: May 21, 1984.
Brief description of amendment: The amendment changes the Technical Specifications for Beaver Valley Unit No. 1 to revise miscellaneous fire protection specifications and their bases.
Date of issuance: January 4, 1985.
Effective date: January 4, 1985.
*Amendment No.:*89.
Facility Operating License No. DPR–66. Amendment revised the Technical Specifications.
Date of initial notice in **Federal Register:** July 24, 1984 (49 FR 29908) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated Janaury 4, 1985.
No significant hazards consideration comments received: None.
Local Public Document Room Location: B. F. Jones Memorial Library, 663 Franklin Avenue, Aliquippa, Pennsylvania 15001.

Georgia Power Company, Oglethorpe Power Corporation, Municipal Electric Authority of Georgia, City of Dalton, Georgia, Docket No. 50–321, Edwin I. Hatch Nuclear Plant, Unit No. 1, Appling County, Georgia

Date of application for amendment: October 18, 1984, supplementing the request of September 5, 1984.
Brief description of amendment: The revision to the Technical Specifications changes the Limiting Conditions for Operation, the surveillance requirements and supporting basis for the High Pressure Coolant Injection Steam Line High Differential Pressure trip function.
Date of issuance: December 27, 1984.
Effective date: December 27, 1984.
Amendment No.: 104.
Facility Operating License No. DPR–57. Amendment revised the Technical Specifications.
Date of initial notice in **Federal Register:** November 21, 1984, 49 FR 45951 The Commission's related evaluation of the amendment is contained in the Safety Evaluation supporting Amendment No. 103 dated December 7, 1984.
No significant hazards consideration comments received: No.
Local Public Document Room location: Appling County Public Library, 301 City Hall Drive, Baxley, Georgia.

GPU Nuclear Corporation, Docket No. 50–219, Oyster Creek Nuclear Generating Station, Ocean County, New Jersey

Date of application for amendment: June 8, 1984.
Brief description of amendment: The amendment to Technical Specifications makes changes to Section 6.0, Administrative Controls.
Date of Issuance: December 27, 1984.
Effective date: December 27, 1984.
Amendment No.: 78.
Provisional Operational License No. DPR–16. Amendment revised the Technical Specifications.
Date of initial notice in **Federal Register:** November 21, 1984 (49 FR 45953). The Commission's related evaluation of this amendment is contained in a Safety Evaluation dated December 27, 1984.
No significant hazards consideration comments received: No.
Local Public Document Room: Ocean County Library, 101 Washington Street. Toms River, New Jersey 08753.

GPU Nuclear Corporation, Docket No. 50–219, Oyster Creek Nuclear Generating Station, Ocean County, New Jersey

Date of application for amendment: August 4, 1983 as supplemented February 8, 1984.

Brief description of amendment: The amendment to Technical Specification, Section 3.1, raises the high drywell pressure setpoint from 2.0 psig to 2.4 psig.

Date of Issuance: January 11, 1985.

Effective date: January 11, 1985.

Amendment No.: 79.

Provisional Operating License No. DPR–16. Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** November 21, 1985 (49 FR 45952). The Commission's related evaluation of this amendment is contained in a Safety Evaluation dated January 11, 1985.

No significant hazards consideration comments received: No.

Local Public Document Room: Ocean County Library, 101 Washington Street, Toms River, New Jersey 08753.

Iowa Electric Light and Power Company, Docket No. 50–331, Duane Arnold Energy Center, Linn County, Iowa

Date of application for amendment: April 6, 1983, as supplemented July 29, 1983, October 17, 1983 and July 25, 1984.

Brief description of amendment: This amendment revises the Technical Specifications to incorporate the Radiological Effluent Technical Specifications (RETS) for Duane Arnold Energy Center (DAEC).

Date of issuance: January 14, 1985.

Effective date: January 1, 1986.

Amendment No.: 109.

Facility Operating License No. DPR–49. Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** August 23, 1983 49 FR 38406 and July 24, 1984 49 FR 29914.

The July 25, 1984 submittal did not change the July 29, 1983, or October 17, 1983 submittals; it requested an effective date of January 1, 1986; therefore no additional notice was issued.

The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated January 14, 1985.

No significant hazards consideration comments received: No.

Local Public Document Room location: Cedar Rapids Public Library, 426 Third Avenue SE., Cedar Rapids, Iowa 52401.

Maine Yankee Atomic Power Company, Docket No. 50–309, Maine Yankee Atomic Power Station, Lincoln County, Maine

Date of application for amendment: June 19, 1984.

Brief description of amendment: The amendment modified the Maine Yankee Technical Specifications to comply with changes to 10 CFR 50.54(m)(2) and (3) and 10 CFR 50.73.

Date of issuance: December 26, 1984.

Effective date: December 26, 1984.

Amendment No.: 79.

Facility Operating License No. DPR–36. Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** August 22, 1984 (49 FR 33353 at 33365).

The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 26, 1984.

No significant hazards consideration comments received: No.

Local Public Document Room Location: Wiscasset Public Library, High Street, Wiscasset, Maine.

Maine Yankee Atomic Power Company, Docket No. 50–309, Maine Yankee Atomic Power Station, Lincoln County, Maine

Date of application for amendment: October 7, 1982 as supplemented September 26, 1983 and May 22, 1984.

Brief description of amendment: This amendment modified the Maine Yankee Technical Specifications concerning containment integrity, to conform more closely with the Standard Technical Specifications.

Date of issuance: December 26, 1984.

Effective date: Within 30 days of the date of its issuance.

Amendment No.: 80.

Facility Operating License No. DPR–36. Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: July 20, 1983 (48 FR 33076), November 22, 1983 (48 FR 52804) and August 22, 1984 (49 FR 33353 at 33365). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 26, 1984.

No significant hazards consideration comments received: No.

Local Public Document Room location: Wiscasset Public Library, High Street, Wiscasset, Maine.

Nebraska Public Power District, Docket No. 50–298, Cooper Nuclear Station, Nemaha County, Nebraska

Date of application for amendment: March 7, 1984, as supplemented April 10, 1984, July 19, 1984 and November 15, 1984.

Brief description of amendment: This amendment revises the Technical Specification to incorporate the Radiological Effluent Technical Specifications (RETS) for Cooper Nuclear Station.

Date of issuance: December 24, 1984.

Effective date: July 1, 1986, except for the following sections of the RETS which are effective January 1, 1985:

a. Section 3.21.F,

b. Section 4.21.F, and

c. Tables 3.21.F.1 and 3.21.F.2 and associated notes.

Amendment No.: 89.

Facility Operating License No. DPR–62. Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: August 23, 1984 48 FR 38404 and November 21, 1984 49 FR 45956.

The November 15, 1984 submittal did not change the March 7, 1984, April 10, 1984, or July 19, 1984 submittals, it provided information to justify the effective dates of implementation; therefore, no additional notice was issued.

The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 24, 1984.

No significant hazards consideration comments received: No.

Local Public Document Room location: Auburn Public Library, 118 15th Street, Auburn, Nebraska 68305.

Nebraska Public Power District, Docket No. 50–298, Cooper Nuclear Station, Nemaha County, Nebraska

Date of application for amendment: February 29, 1984, as supplemented July 18, 1984.

Brief description of amendment: The amendment revises the Technical Specifications to (1) incorporate changes proposed in response to TMI Action Plan Items set forth in NUREG–0737, "Clarification of TMI Action Plan Requirements" and requested by the staff's Generic Letter 83–36, (2) add four additional fire detectors located near the service water pumps to the list of fire detection instruments in Table 3.14 and correct the indentification numbers of two fire detectors listed in that table, and (3) clarify a setpoint on Table 3.2.B for the Reactor Core Isolation Cooling System.

Date of issuance: January 3, 1985.

Effective date: January 3, 1985.

Amendment No.: 90.

Facility Operating License No. DPR–62. Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: May 23, 1984 49 FR 21831 and September 28, 1984 49 FR 38402.

The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated January 3, 1985.

No significant hazards consideration comments received: No.

Local Public Document Room location: Auburn Public Library, 118 15th Street, Auburn, Nebraska 68305.

Pennsylvania Power & Light Company, Docket No. 50–387, Susquehanna Steam Electric Station, Unit 1, Luzerne County, Pennsylvania

Date of applications for amendment: December 8, 1983 and May 3, 1984.

Brief description of amendment: This amendment changes License Condition 2.G. of Facility Operating License No. NFP–14 to be consistent with NRC rule changes effective January 1, 1984. This amendment also incorporates Change S to the Physical Security Plan into License Condition 2.D.

Date of issuance: December 20, 1984.

Effective date: December 20, 1984.

Amendment No.: 27.

Facility Operating License No. 14: Amendment revised License Conditions.

Date of initial notice in **Federal Register:** May 23, 1984 (21833–21834) and September 28, 1984 (38406–38407), respectively. The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 20, 1984.

No significant hazards consideration comments received: No.

Local Public Document Room location: Osterhout Free Library, Reference Department, 71 South Franklin Street, Wilkes-Barre, Pennsylvania 18701.

Pennsylvania Power & Light Company, Docket No. 50–388, Susquehanna Steam Electric Station, Unit 2, Luzerne County, Pennsylvania

Date of applications for amendment: May 3, 1984.

Brief description of amendment: This amendment changes License Condition 2.D. of Facility Operating License No. NFP–22 to incorporate Change S to the Physical Security Plan.

Date of issuance: December 20, 1984.

Effective date: December 20, 1984.

Amendment No.: 4

Facility Operating License No. 22: Amendment revised License Conditions.

Date of initial notice in Federal Register: September 28, 1984 (38406–38407). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 20, 1984.

No significant hazards consideration comments received: No.

Local Public Document Room location: Osterhout Free Library, Reference Department, 71 South Franklin Street, Wilkes-Barre, Pennsylvania 18701.

Portland General Electric Company, et al. Docket No. 50–344, Trojan Nuclear Plant, Columbia County, Oregon

Date of application for amendment: January 28, 1983, supplemented March 27, 1984.

Brief description of amendment: The amendment makes numerous changes to the Radiological Effluent Technical Specifications (RETS) to comply with Appendix I of 10 CFR Part 50 developed for the purpose of keeping releases of radioactive materials to unrestricted areas as low as is reasonably achievable.

Date of issuance: December 20, 1984.

Effective date: January 1, 1985.

Amendment No.: 99

Facility Operating License No. NPF–1. Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** July 20, 1983, (48 FR 33076 at 33085) and September 28, 1984 (49 FR 38390 at 38407). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 20, 1984.

No significant hazards consideration comments received: No comments received.

Location of Local Public Document Room: Multnomah County Library, 801 SW. 10th Avenue, Portland, Oregon.

Portland General Electric Company, et al., Docket No. 50–344, Trojan Nuclear Plant, Columbia County, Oregon

Date of application for amendment: December 28, 1983.

Brief description of amendment: The amendment revises Table 6.2–1, "Minimum Shift Crew Composition", to allow the duties of the Shift Technical Advisor and licensed Senior Operator to be combined.

Date of issuance: January 9, 1985.

Effective date: January 9, 1985.

Amendment No.: 100.

Facility Operating License No. NPF–1: Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: January 26, 1984 (49 FR 3351). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated January 9, 1985.

No significant hazards consideration comments received: No comments received.

Location of Local Public Document Room: Multnomah County Library, 801 SW. 10th Avenue, Portland, Oregon.

Public Service Company of Colorado, Docket No. 50–267, Fort St. Vrain Nuclear Generating Station, Platteville, Colorado

Date of application for amendment: September 27, 1984.

Brief description of amendment: Changes the fire hose stations numbering sequence as shown in Table 4.10–7 of the Technical Specifications to provide a sequence which uniquely identifies the location of the station.

Date of issuance: January 3, 1985.

Effective date: January 3, 1985.

Amendment No.: 46.

Facility Operating License No. DPR–34: Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: November 21, 1984 (49 FR 45963). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated January 3, 1985.

No significant hazards consideration comments received: No.

Local Public Document Room location: Greeley Public Library, City Complex Building, Greeley, Colorado.

Rochester Gas and Electric Corporation, Docket No. 50–244, R. E. Ginna Nuclear Power Plant, Wayne County, New York

Date of application for amendment: August 30, 1984.

Brief description of amendment: The amendment modifies the March 14, 1983 Confirmatory Order regarding items set forth in NUREG–0737 for which the staff requested completion on or after July 1, 1981. The schedule for completion of Item III.D.3.4, Control Room Habitability, is changed from July 1984 to September 30, 1984.

Date of issuance: December 20, 1984.

Effective date: December 20, 1984.

Amendment No.: 10

Facility Operating License No. DPR–18. Amendment revised the license.

Date of initial notice in Federal Register: October 24, 1984 (49 FR 42829).

The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 20, 1984.

No significant hazards consideration comments received: No.

Local Public Document Room location: Rochester Public Library, 155 South Avenue, Rochester, New York 14604.

South Carolina Electric & Gas Company, South Carolina Public Service Authority, Docket No. 50–395, Virgil C. Summer Nuclear Station, Unit 1, Fairfield County, South Carolina.

Date of application for amendment: February 22, 1984.

Brief description of amendment: The amendment modifies the Technical Specification reporting requirements to be in accordance with new regulation 10 CFR 50.73.

Date of issuance: January 2, 1985.

Effective date: January 2, 1985.

Amendment No.: 35.

Facility Operating License No. NPF–12. Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: September 28, 1984 (49 FR 38408) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated January 2, 1985.

No significant hazards consideration comment received: No.

Local Public Document Room location: Fairfield County Library, Garden and Washington Streets, Winnsboro, South Carolina 29180.

Southern California Edison Company, et al. Docket Nos. 50–361 and 50–362, San Onofre Nuclear Generating Station, Units 2 and 3, San Diego County, California

Dates of application for amendments: April 6 and 27, September 11, 1984.

Brief description of amendments: The amendments change Technical Specification 3/4.3.2 concerning control room toxic gas isolation system setpoints.

Date of issuance: January 9, 1985.

Effective date: January 9, 1985.

Amendment Nos.: 29 and 18.

Facility Operating License Nos. NPF–10 and NPF–15: Amendments revised the Technical Specifications.

Dates of initial notices in Federal Register: September 28, 1984 (49 FR 38409). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated January 9, 1985.

No significant hazards consideration comments were received.

Local Public Document Room Location: San Clemente Library, 242 Avenida Del Mar, San Clemente, California.

Southern California Edison Company, et al. Docket Nos. 50–361 and 50–362, San Onofre Nuclear Generating Station, Units 2 and 3, San Diego County, California

Dates of application for amendments: April 10, August 1 and 7, 1984.

Brief description of amendments: The amendments change Technical Specification 3.1.3, "Movable Control Element Assemblies," to (1) require a reduction in core power after the detection of a CEA deviation, (2) require that the regulating CEA groups be limited to the Short Term Steady State Insertion Limits when COLSS is out of service, and (3) restrict part length CEA positions to the core power dependent insertion limits.

Date of issuance: January 9, 1985.

Effective date: January 9, 1985.

Amendment Nos.: 30 and 19.

Facility Operating License Nos. NPF–10 and NPF–15: Amendments revised the Technical Specifications.

Dates of initial notices in **Federal Register:** October 24, 1984 (49 FR 42831). The Commission's related evaluation of the amendment is contained in a Safety evaluation dated January 9, 1985. No significant hazards consideration comments were receive.

Local Public Document Room Location: San Clemente Library, 242 Avenida Del Mar, San Clemente, California.

Southern California Edison Company, et al. Docket Nos. 50–361 and 50–362, San Onofre Nuclear Generating Station, Units 2 and 3, San Diego County, California

Dates of application for amendments: March 2 and April 2, 1984.

Brief description of amendments: The amendments change Technical Specifications relating to radiation and radioactive effluent monitoring instrumentation.

Date of issuance: January 11, 1985.

Effective date: January 11, 1985.

Amendment Nos.: 31 and 20.

Facility Operating License Nos. NPF–10 and NPF–15: Amendments revised the Technical Specifications.

Dates of initial notices in **Federal Register:** November 21, 1984 (49 FR 45969). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated January 11, 1985.

No significant hazards consideration comments were received.

Local Public Document Room Location: San Clemente Library, 242 Avenida Del Mar, San Clemente, California.

Virginia Electric and Power Company, et al., Docket Nos. 50–338 and 50–339, North Anna Power Station, Units No. 1 and 2, Louisa County, Virginia

Date of application for amendment: August 20, 1982, supplemented by letters dated October 21, 1982, June 16, 1983, July 25, 1983, September 13, 1983, October 28, 1983, November 10, 1983, December 6, 1983, April 10, 1984, May 8, 1984 and May 18, 1984.

Brief description of amendment: The amendments revise the capacity of the Spent Fuel Storage Pool at NA–1&2. Specifically, the NA–1&2 Technical Specification 5.6.1 identifies a new nominal center-to-center spacing between fuel assemblies of 10 and 9/16 inches. In addition, the NA–1&2 TS 5.6.3 is revised to modify the spent fuel storage capacity to 1737 fuel assemblies. Finally, the amendments revise the NA–1&2 TS 5.6.1 and 5.6.3 to be identical with the NRC approved TS 5.6.1 and 5.6.3 in order to provide consistency between the NA–1&2 TS.

Date of issuance: December 21, 1984.

Effective date: December 21, 1984.

Amendment Nos. 61 and 45.

Facility Operating License Nos. NPF–4 and NPF–7. Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** September 22, 1982 (47 FR 41893) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 2, 1984 and an Environmental Assessment dated July 2, 1984.

No significant hazards consideration comments received: Yes.

(1) Petition to intervene of Louisa County, Virginia and Board of Supervisors of Louisa County, Virginia dated October 22, 1982.

(2) Petition to intervene of Concerned Citizens of Louisa County, Virginia dated October 22, 1982.

Disposition of above Petitions:

(1) By Order dated May 22, 1984 the Atomic Safety and Licensing Board granted Louisa County's request for withdrawal as an intervening party in Case OLA–2 (expansion of the spent fuel storage capacity for North Anna Units 1 & 2.)

(2) By Memorandum and Order dated October 15, 1984, the Atomic Safety and Licensing Board denied Concerned Citizens of Louisa County's petition for leave to intervene in Case OLA–2. The Board order authorized the Director of Nuclear Reactor Regulation to issue amendments to Facility Operating Licenses No. NPF–4 and No. NPF–7 which permit expansion of the spent fuel storage for North Anna Units 1 & 2 from 966 to 1737 fuel assemblies.

(3) By Memorandum and Order dated November 20, 1984, the Atomic Safety and Licensing Appeal Board ruled that Concerned Citizens of Louisa County's appeal from the Licensing Board's Memorandum and Order of October 15, 1984 in Case OLA–2 was dismissed.

Local Public Document Room locations: Board of Supervisors Office, Louisa County Courthouse, Louisa, Virginia 23093 and the Alderman Library, Manuscripts Department, University of Virginia, Charlottesville, Virginia 22901.

Wisconsin Electric Power Company, Docket Nos. 50–266 and 50–301, Point Beach Nuclear Plant, Unit Nos. 1 and 2, Town of Two Creeks, Manitowoc County, Wisconsin

Date of application of amendments: September 25, 1984.

Brief description of amendments: The amendments change the effective date of previously issued amendments 84 and 88 to Facility Operating Licenses DPR–24 and DPR–27 as indicated below.

Date of issuance: December 27, 1984.

Effective date: Upon completion of equipment installation and testing but not later than March 1, 1985.

Amendment Nos.: 87 and 92.

Facility Operating License Nos. DPR–24 and DPR–27. Amendments revised the effective date of Amendments 84 and 88.

Date of initial notice in **Federal Register:** November 21, 1984, 49 FR 45941 at 45981.

The Commission's related evaluation of the amendments is contained in a Safety Evaluation dated December 27, 1984.

No significant hazards consideration comments received: No.

Local Public Document Room location: Joseph P. Mann Library, 1516 Sixteenth Street, Two Rivers, Wisconsin.

Wisconsin Public Service Corporation, Docket No. 50–305, Kewaunee Nuclear Power Plant, Kewaunee County, Wisconsin

Date of application for amendment September 13, 1984.

Brief description of amendment: Deletes list of snubbers from plant Technical Specifications and includes other minor snubber related changes.

Date of issuance: December 26, 1984.

Effective date: December 26, 1984.

Amendment No. 57.

Facility Operating License No. DPR–43: Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** November 21, 1984 (49 FR 45982) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated December 26, 1984.

Significant hazards consideration comments received: None.

Local Public Document Room location: University of Wisconsin, Library Learning Center, 2420 Nicolet Drive, Green Bay, Wisconsin 54301.

Wisconsin Public Service Corporation, Docket No. 50–305, Kewaunee Nuclear Power Plant, Kewaunee County, Wisconsin

Date of application for amendment: July 27, 1984.

Brief description of amendment: Revision of reporting requirements to conform with amended NRC Regulations 10 CFR 50.72 and 10 CFR 50.73.

Date of issuance: January 4, 1985.

Effective date: January 4, 1985.

Amendment No: 58.

Facility Operating License No. DPR–43: Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** September 28, 1984 (49 FR 38414)

The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated January 4, 1985.

Significant hazards consideration comments received: None.

Local Public Document Room location: University of Wisconsin, Library Learning Center, 2420 Nicolet Drive, Green Bay, Wisconsin 54301.

Wisconsin Public Service Corporation, Docket No. 50–305, Kewaunee Nuclear Power Plant, Kewaunee County, Wisconsin

Date of application for amendment: March 30, 1984.

Brief description of amendment: Licensee response to NRC Generic Letter 83–37 wherein we requested proposed Technical Specifications for certain NUREG–0737 installed features.

Date of issuance: January 9, 1985.

Effective date: Sixty days from date of issuance of license amendment.

Amendment No. 59.

Facility Operating License No. DPR–43: Amendment revised the Technical Specifications.

Date of initial notice in **Federal Register:** May 23, 1984 (49 FR 21850) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated January 9, 1985.

Significant hazards consideration comments received: None.

Local Public Document Room location: University of Wisconsin, Library Learning Center, 2420 Nicolet Drive, Green Bay, Wisconsin 54301.

OTHER NOTICES: NOTICE OF ISSUANCE OF AMENDMENT PURSUANT TO INITIAL DECISION OF ATOMIC SAFETY AND LICENSING BOARD FOR WHICH A FINAL DETERMINATION OF NO SIGNIFICANT HAZARDS CONSIDERATION WAS NOT REQUIRED

GPU Nuclear Corporation, et al., Docket No. 50–289, Three Mile Island Nuclear Station, Unit No. 1, Dauphin County, Pennsylvania

Date of amendment request: May 9, 1983.

Brief description of amendment: This amendment permits the return to operation of the repaired steam generators. On August 25, 1983, the Commission issued Amendment No. 86 (48 FR 39709) which addressed a portion of the licensees' application of May 9, 1983. That amendment revised the TSs to recognize and approve the steam generator tube kinetic expansion repair technique as an alternative to plugging of defective tubes, only for purposes of steam generator hot functional testing using pump heat (non-nuclear), and permitted such testing. Similarly, Amendment No. 91, issued on April 9, 1984, further modified TS 4.19 to cover the total period of pre-critical (non-nuclear) hot functional testing of the plant.

This amendment completes the Commission's action on the May 9 application by further modifying the TSs to remove restrictions as to the period of effectiveness of the acceptability of the kinetic expansion repair process as an alternative to plugging defective tubes in the steam generators, thus permitting them to return to operation. The TSs are further modified to add requirements regarding the condenser offgas radiation monitor. In addition, conditions have been added to the license to require primary-to-secondary leakage restrictions, power ascension test program results availability, extended inservice inspection, evaluation of operational leakage, and reporting corrosion lead tests.

Notice of Consideration of Issuance of Amendment and Proposed No Significant Hazards Consideration Determination and Opportunity for Hearing in connection with this action was published in the **Federal Register** on May 31, 1983 (48 FR 24231), and corrected June 14, 1983 (48 FR 27328). In response to this notice, requests for hearing were filed by TMIA on May 19, 1983, as amended on June 23, 1983, and by Lee, Molholt, and Aamodt on June 30, 1983, as amended on July 13, 1983.

Comments were made by six other persons and the Commonwealth of Pennsylvania.

On August 25, 1983, the Commission issued a Safety Evaluation (NUREG–1019) related to this action and reopened the comment period to receive further public comments on the proposed no significant hazards consideration published on May 31. A "Notice of Additional Opportunity for Comment" was published in the Federal Register on August 31, 1983 (48 FR 39541). Additional comments were filed by the Commonwealth of Pennsylvania.

A hearing was held on July 16–18, 1984, and the Atomic Safety and Licensing Board issued its Initial Decision on October 31, 1984.

Date of issuance: December 21, 1984.

Effective date: December 21, 1984.

Amendment No. 103.

Facility Operating License No. DPR–50. Amendment revised the license and the Technical Specifications.

Date of initial notice in Federal Register: January 4, 1985, 50 FR 580.

NOTICE OF ISSUANCE OF AMENDMENT TO FACILITY OPERATING LICENSE AND FINAL DETERMINATION OF NO SIGNIFICANT HAZARDS CONSIDERTION AND OPPORTUNITY FOR HEARING (EXIGENT OR EMERGENCY CIRCUMSTANCES)

During the 30-day period since publication of the last monthly notice, the Commission has issued the following amendments. The Commission has determined for each of these amendments that the application for the amendment complies with the standards and requirements of the Atomic Energy Act of 1954, as amend (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Chapter I, which are set forth in the license amendment.

Because of exigent or emergency circumstances associated with the date the amendment was needed, there was not time the Commission to publish, for public comment before issuance, its usual 30-day Notice of Consideration of Issuance of Amendment and Proposed No Significant Hazards Consideration Determination and Opportunity for Hearing. For exigent circumstances, a press release seeking public comment as to the proposed no significant hazards consideration determination was used, and the State was consulted by telephone. In circumstances where failure to act in a timely was would have resulted, for example, in derating or shutdown of a nuclear power plant, a shorter public comment period (less than 30 days) has been offered and the State consulted by telephone whenever possible.

Under its regulations, the Commission may issue and make an amendment immediately effective, notwithstanding the pendency before it of a request for a hearing from any person, in advance of the holding and completion of any required hearing, where it has determined that no significant hazards consideration is involved.

The Commission has applied the standards of 10 CFR 50.92 and has made a final determination that the amendment involves no significant hazards consideration. The basis for this determination is contained in the documents related to this action. Accordinaly, the amendments have been issued and made effective as indicated.

Unless otherwise indicated, the Commission has determined that these amendments satisfy the criteria for categorical exclusion in accordance with 10 CFR 51.22. Therefore, pursuant to 10 CFR 51.22(b), no environmental impact statement or environmental assessment need be prepared for these amendments. If the Commission has prepared an environmental assessment under the special circumstances provision in 10 CFR 51.12(b) and has made a determination based on that assessment, it is so indicated.

For further details with respect to the action see (1) the application for amendment, (2) the amendment to Facility Operating License, and (3) the Commission's related letter, Safety Evaluation and/or Environmental Assessment, as indicated. All of these items are available for public inspection at the Commission's Public Document Room, 1717 H Street NW., Washington, D.C., and at the local public document room for the particular facility involved.

A copy of items (2) and (3) may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Licensing.

The Commission is also offering an opportunity for a hearing with respect to the issuance of the amendments. By February 22, 1985, licensee may file a request for a hearing with respect to issuance of the amendment to the subject facility operating license and any person whose interest may be affected by this proceeding and who wishes to participate as a party in the proceeding must file a written petition for leave to intervene. Requests for a hearing and petitions for leave to intervene shall be filed in accordance with the Commission's "Rules of Practice for Domestic Licensing Proceedings" in 10 CFR Part 2. If a request for a hearing or petition for leave to intervene is filed by the above date, the Commission or an Atomic Safety and Licensing Board, designated by the Commission or by the Chairman of the Atomic Safety and Licensing Board Panel, will rule on the request and/or petition and the Secretary or the designated Atomic Safety and Licensing Board will issue a notice of hearing or an appropriate order.

As required by 10 CFR 2.714, a petition for leave to intervene shall set forth with particularity the interest of the petitioner in the proceeding and how that interest may be affecteded by the results of the proceeding. The petition should specifically explain the reasons why intervention should be permitted with particular reference to the following factors: (1) The nature of the petitioner's right under the Act to be made a party to the proceeding; (2) the nature and extent of the petitioner's property, financial, or other interest in the proceeding; and (3) the possible effect of any order which may be entered in the proceeding on the petitioner's interest. The petition should also identify the specific aspect(s) of the subject matter of the proceeding as to which petitioner wishes to intervene. Any person who has filed a petition for leave to intervene or who has been admitted as a party may amend the petition without requesting leave of the Board up to fifteen (15) days prior to the first prehearing conference scheduled in the proceeding, but such an amended petition must satisfy the specificity requirements decribed above.

Not later than fifteen (15) days prior to the first prehearing conference scheduled in the proceeding, a petitioner shall file a supplement to the petition to intervene which must include a list of the contentions which are sought to be litigated in the matter, and the bases for each contention set forth with reasonable specificity. Contentions shall be limited to matters with the scope of the amendment under consideration. A petitioner who fails to file such a supplement which satisfies these requirements with respect to at least one contention will not be permitted to participate as a party.

Those permitted to intervene become parties to the proceeding, subject to any limitations in the order granting leave to intervene, and have the opportunity to participate fully in the conduct of the hearing, including the opportunity to present evidence and cross-examine witnesses.

Since the Commission has made a final determination that the amendment involves not significant hazards consideration, if a hearing is requested, it will not stay the effectiveness of the amendment. Any hearing held would take place while the amendment is in effect.

A request for a hearing or a petition for leave to intervene must be filed with the Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Docketing and Service Branch, or may be delivered to the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C. by the above date. Where petitions are filed during the last ten (10) days of the notice period, it is requested that the petitioner promptly so inform the Commission by a toll-free telephone call to Western Union at (800) 325–6000 (in Missouri (800) 342–6700). The Western Union operator should be given Datagram Identification Number 3737 and the followng message addressed to (*Branch Chief*): petitioner's name and telephone number; date petition was mailed; plant name; and publication date and page number of this **Federal Register** notice. A copy of the petition should also be sent to the Executive Legal Director, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, and to the attorney for the licensee.

Nontimely filings of petitions for leave to intervene, amended petitions, supplemental petitions and/or requests for hearing will not be entertained absent a determination by the Commission, the presiding officer or the Atomic Safety and Licensing Board designated to rule on the petition and/or request, that the petitioner has made a substantial showing or good cause for the granting of a late petition and/or request. That determination will be based upon a balancing of the factors specified in 10 CFR 2.714(a)(1)(i)–(v) and 2.714(d).

The Toledo Edison Company and The Cleveland Electric Illuminating Company, Docket No. 50–346, Davis-Besse Nuclear Power station, Unit No. 1, Ottawa County, Ohio

Date of application for amendment: December 3, 1984.

Brief description of amendment: This amendment modifies TS Section 1.6, which provides the definition of OPERABLE—OPERABILITY, so that from the effective date of this amendment to until Mode 1 is entered for Cycle 5 only, operability of the auxiliary feedwater system will be determined without consideration of the status of the startup feedwater system.

Date of issuance: December 20, 1984.

Effective date: December 20, 1984.

Amendment No.: 82.

Facility Operating License No. NPF–3. Amendment revised the Technical Specifications.

Public comments requested as to proposed no significant hazards consideration: Yes, by Legal Ad published in the *Toledo Blade* on December 8, 1984, the Fremont, Ohio, *News Messenger* on December 13, 1984, and in the Port Clinton, Ohio, *News Herald* on December 12, 1984.

Comments received: No.

The Commission's related evaluation of the amendment, finding of exigent circumstances, and final determination of no significant hazards consideration are contained in a Safety Evaluation dated December 20, 1984

Attorney for licensee: Gerald Charnoff, esq., Shaw, Pittman, Potts, and Trowdridge, 1800 M Street NW., Washington, D.C. 20036.

Local Public Document Room location: University of Toledo Library. Documents Department, 2801 Bancroft Avenue, Toledo, Ohio 43606.

Dated at Bethesda, Maryland this 16th day of January 1985.

For the Nuclear Regulatory Commission.

Donald E. Sells,

Acting Chief, Operating Reactors Branch No. 3, Division of Licensing.

[FR Doc. 85–1627 Filed 1–22–85; 8:45 am]

BILLING CODE 7590-01-M

Draft Regulatory Guide; Issuance and Availability

The Nuclear Regulatory Commission has issued for public comment a draft of a new guide planned for its Regulatory Guide Series together with a draft of the associated value/impact statement. This series has been developed to describe and make available to the public methods acceptable to the NRC staff of implementing specific parts of the Commission's regulations and, in some cases, to delineate techniques used by the staff in evaluating specific problems or postulated accidents and to provide guidance to applicants concerning certain of the information needed by the staff in its review of applications for permits and licenses.

The draft, temporarily identified by its task number, SG 302–4 (which should be mentioned in all correspondence concerning this draft guide), is entitled "Vital Islands, Protection of Physical Security Equipment, and Key and Lock Controls" and is intended for Division 5, "Materials and Plant Protection." It is being developed to present approaches that would be acceptable to the NRC staff for implementing proposed amendments to 10 CFR Part 73 (49 FR 40735) if they are promulgated in their present form. Emphasis in the guide is on minimizing the safeguards impact on safety.

This draft guide and the associated value/impact statement are being issued to involve the public in the early stages of the development of a regulatory position in this area. They have not received complete staff review and do not represent an official NRC staff position.

Public comments are being solicited on both drafts, the guide (including any implementation schedule) and the draft value/impact statement. Comments on the draft value/impact statement should be accompanied by supporting data. Comments on both drafts should be sent to the Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, DC 20555, Attention: Docketing and Service Branch, by March 7, 1985.

Although a time limit is given for comments on these drafts, comments and suggestions in connection with (1) items for inclusion in guides currently being developed or (2) improvements in all published guides are encouraged at any time.

Regulatory guides are available for inspection at the Commission's Public Document Room, 1717 H Street NW., Washington, D.C. Requests for single copies of draft guides (which may be reproduced) or for placement on an automatic distribution list for single copies of future draft guides in specific divisions should be made in writing to the U.S. Nuclear Regulatory Commission, Washington, DC 20555, Attention: Director, Division of Technical Information and Document Control. Telephone requests cannot be accommodated. Regulatory guides are not copyrighted, and Commission approval is not required to reproduce them.

(5 U.S.C. 552(a))

Dated at Rockville, Maryland this 15th day of January 1985.

For the Nuclear Regulatory Commission.

Frank P. Gillespie,

Director, Division of Risk Analysis and Operations, Office of Nuclear Regulatory Research.

[FR Doc. 85–1727 Filed 1–22–85; 8:45 am]

BILLING CODE 7590-01-M

Advisory Committee on Reactor Safeguards; Subcommittee on Watts Bar; Meeting

The ACRS Subcommittee on Watts Bar will hold a meeting on February 13, 1985, Ramada Inn West, 7621, Kingston Pike, Knoxville, TN.

The entire meeting will be open to public attendance.

The agenda for subject meeting shall be as follows:

Wednesday, February 13, 1985—8:30 a.m. until the conclusion of business

The Subcommittee will discuss major open items prior to fuel load and to update the Subcommittee concerning modifications to the Model D–3 steam generators, the fire protection program, and resolution of construction and QA deficiencies.

Oral statements may be presented by members of the public with concurrence of the Subcommittee Chairman; written statements will be accepted and made available to the Committee. Recordings will be permitted only during those portions of the meeting when a transcript is being kept, and questions may be asked only by members of the Subcommittee, its consultants, and Staff. Persons desiring to make oral statements should notify the ACRS staff member named below as far in advance as practicable so that appropriate arrangements can be made.

During the initial portion of the meeting, the Subcommittee, along with any of its consultants who may be present, will exchange preliminary views regarding matters to be considered during the balance of the meeting.

The Subcommittee will then hear presentations by and hold discussions with representatives of the NRC Staff, their consultants, and other interested persons regarding this review.

Further information regarding topics to be discussed, whether the meeting has been cancelled or rescheduled, the Chairman's ruling on requests for the opportunity to present oral statements and the time allotted therefor can be obtained by a prepaid telephone call to the cognizant ACRS staff member, Mr. Anthony Cappucci (telephone 202/634–3267) between 8:15 a.m. and 5:00 p.m., EST. Persons planning to attend this meeting are urged to contact the above named individual one or two days before the scheduled meeting to be advised of any changes in schedule, etc., which may have occurred.

Dated: January 16, 1985.

Morton W. Libarkin,

Assistant Executive Director for Project Review.

[FR Doc. 85–1725 Filed 1–22–85; 8:45 am]

BILLING CODE 750-01-M

Advisory Committee on Reactor Safeguards; Proposed Meetings

In order to provide advance information regarding proposed public meetings of the ACRS Subcommittees and meetings of the full Committee, the following preliminary schedule is published to reflect the current situation, taking into account additional meetings which have been scheduled and meetings which have been postponed or cancelled since the last list of proposed meetings published December 24, 1984 (49 FR 49953). Those meetings which are definitely scheduled have had, or will have, an individual notice published in the **Federal Register** approximately 15 days (or more) prior to the meeting. It is expected that the sessions of the full Committee meeting designated by an asterisk (*) will be open in whole or in part to the public. ACRS full Committee meetings begin at 8:30 a.m. and Subcommittee meetings usually begin at 8:30 a.m. The time when items listed on the agenda will be discussed during full Committee meetings and when Subcommittee meetings will start will be published prior to each meeting. Information as to whether a meeting has been firmly scheduled, cancelled, or rescheduled, or whether changes have been made in the agenda for the February 1985 ACRS full Committee meeting can be obtained by a prepaid telephone call to the Office of the Executive Director of the Committee (telephone 202/634–3267, ATTN: Barbara Jo White) between 8:15 a.m. and 5:00 p.m., Eastern Time.

ACRS Subcommittee Meetings

Braidwood Station, January 29, 1985, Washington, DC. The Subcommittee will continue to review the Commonwealth Edison Company's application for an operating license for Braidwood.

Fire Protection, February 5, 1985, Washington, DC. The Subcommittee will be briefed on the following: (1) The status of Appendix R compliance, (2) Duke and Calvert Cliffs compliance with Appendix R, (3) fire insurance companies' views on fire protection, and (4) the status of fire protection research at Sandia.

Advanced Reactors, February 5, 1985, Washington, DC. The Subcommittee will discuss the DOE's redirected programs for LMRs and to review the relevant NRC research programs in the areas of LMRs and HTGRs.

Regulatory Policies and Practices, February 6, 1985, Washington, DC. The Subcommittee will review the Commission's proposed Backfitting Rule.

Watts Bar, February 13, 1985, Knoxville, TN. The Subcommittee will discuss major open items prior to fuel load and to update the Subcommittee concerning modifications of the Model D-3 steam generators, the fire protection program, and resolution of construction and QA deficiencies.

Combined GESSAR II and Reliability & Probabilistic Assessment, February 14 and 15, 1985, Los Angles, CA. The Subcommittee will continue their review of GESSAR II for a Final Design Approval applicable to future plants. The focus of this meeting will be on seismic risk.

Nine Mile Point Unit 2, February 20 and 21, 1985, Syracuse, NY. The Subcommittee will begin review of the Niagara Mohawk Power Corporation's application for an operating license for Nine Mile Point Unit 2.

Emergency Core Cooling Systems, February 21, 1985, Washington, DC. The Subcommittee will review provisions of proposed Rule to revise Appendix K to 10 CFR 50.46 and discuss proposed Regulatory Guide 1.82, "Containment Emergency Sump Performance" (tentative).

Class 9 Accidents, February 25, 1985, Washington, DC. The Subcommittee will discuss with the NRC Staff the status of the NRC's severe accident codes.

Emergency Core Cooling Systems, Date to be determined (late February/early March), Washington, DC. The Subcommittee will continue the review of Yankee Atomic's request for an exemption to Appendix K of 10 CFR 50.46.

Maintenance Practices and Procedures, March 5, 1985, Washington, DC. The subcommittee will review staff Maintenance Program Plan.

Safety Philosophy, Technology, and Criteria, March 6, 1985, Washington, DC. The Subcommittee will review the status of the NRC Staff's evaluation of the trial use of the Commission's proposed Safety Goal Policy.

Regulatory Policies and Practices, March 6, 1985, Washington, DC. The Subcommittee will continue the review of NRC report on the need for an "NTSB-like" board in the NRC.

Class 9 Accidents, March 14, 1985, Washington, DC. The Subcommittee will discuss New York Power Authority's Source Term studies.

ATWS, March 15, 1985, Washington, DC. The Subcommittee will review the

NRC Staff's activities associated with implementation of the ATWS rule.

Reliability Assurance, March 19, 1985 (tentative), Washington, DC. The Subcommittee will review concerns arising from a significant failure of an RCIC steam line isolation valve to open against operating reactor pressure.

Electrical Systems, March 20, 1985, Washington, DC. The Subcommittee will discuss recent plant experience with the loss of AC power and the status of NRC action on USI A–44, "Station Blackout", and the status of recent NRC actions on diesel generator reliability.

Combined Extreme External Phenomena, Structural Enginering, and Diablo Canyon, March 21 and 22, 1985, Los Angles, CA. The Subcommittees will discuss the status of the NRC Staff seismic design margins programs and PG&E's plan for a seismic reevaluation of Diablo Canyon.

Safeguards and Security, March 27, 1985, Albuquerque, NM. The Subcommittee will review design features for protection against sabotage at commercial nuclear power reactors, explore the potential consequences of successful sabotage at nonpower reactors, and hear how the NRC Staff reviews and evaluates licensees' security plans.

Combine GESSAR II and Reliability & Probabilistic Assessment, March 27, 28, and 29, 1985, Albuquerque, NM. The Subcommittees will continue their review of GESSAR II for a Final Design Approval applicable to future plants. The principal topics to be discussed are plant safeguards and the GESSAR II probabilistic risk assessment.

Air Systems, Date to be detemined (late March), Washington, DC. The Subcommittee will review the NRC's Supplement to the Control Room Habitability Working Group Report. This Supplement is to discuss the Staff's survey of near term operating license and operating reactor control rooms.

Human Factors, Date to be determined (late March), Washington, DC. The Subcommittee will discuss NUREG/CR–3737, a method of ascertaining management/organization's contribution to the safety of operating reactors.

Combined Metal Components and Seismic Design of Piping, Date to be determined (March, tentative), Washington, DC. The Subcommittees will review the NRC piping Review Committee's overall recommendation on piping system concerns.

Qualification Program for Safety-Related Equipment, Date to be determined (March, tentative), Washington, DC. The Subcommittee will discuss the NRC Staff's resolution of USI A–46, "Seismic Qualification of Equipment in Operating Plants."

Seismic Design of Piping, Date to be determined (March, tentative), Washington, DC. The Subcommittee will review draft reports issued by the NRC Piping Review Committee on dynamic loads and load combinations and seismic design requirements of piping.

River Bend Nuclear Power Plant Units 1 and 2, April 10, 1985, Washington, DC. The Subcommittee will continue the review of Gulf States Utilities application for an operating license for the River Bend Nuclear Power Plants Units 1 and 2.

Emergency Core Cooling Systems, Date to be determined (early spring), Palo Alto, CA. The Subcommittee will continue the review of the joint NRC/B&W Owners Group/EPRI/B&W joint IST Program. A visit to the EPRI Stanford Research Institute facilities supporting this Program is also planned.

Palo Verde Nuclear Generating Station, Date to be determined, Maricopa County, AZ. The subcommittee will review the final reports for various construction deficiencies and the results of the preoperational testing as requested in ACRS letter dated December 15, 1981

Waste Management, Date to be determined, Washington, DC. The Subcommittee will review DOE's Final Mission Plan for Civilian Radioactive Waste Management Program.

Combined Reliability and Probabilistic Assessment and Millstone 3, Date and location to be determined. The Subcommittees will review the probabilistic risk assessment for Millstone 3.

Combined Reactor Operations and Human Factors, Date and location to be determined. The Subcommittees will discuss INPO evaluation of nuclear plant operations and incidents/accidents—briefing by INPO representatives.

ACRS Full Committee Meeting

February 7–9, 1985: Items are *tentatively* scheduled.

*A. *Backfitting of Nuclear Plans*—Review proposed NRC revision to 10 CFR Part 50 backfitting requirements.

*B. *NRC Safety Research Program and Budget*—ACRS report to the U.S. Congress regarding the proposed NRC safety research program and budget for FY 1986 and 1987.

*C. *Braidwood Nuclear Plant Units 1 and 2*—Review request for proposed operation of this plant.

*D. *Meeting with NRC Commissioners*—Discuss ACRS activities regarding safety related and regulatory activities including proposed use of the "check-operator" concept for licensed nuclear power plant operators.

*E. *Pressurized Thermal Shock*—Discuss comments by NRC Staff member regarding regulatory requirements to prevent damage to reactor pressure vessels from pressurized thermal shock.

*F. *Institute for Nuclear Power Operations*—Briefing regarding activities of INPO in review and evaluation of nuclear power plant operations and incidents.

*G. *Fire Protection at Nuclear Facilities*—Discuss report of NRC Task Force on implementation of fire protection requirements (10 CFR Part 50, Appendix R) at nuclear power plants.

*H. *Anticipated Transients Without Scram*—Briefing and discussion regarding BNL study of anticipated transients without scram with consequential failures.

*I. *Decay Heat Removal*—Briefing and discussion regarding proposed NRC Staff activity regarding resolution of USI A–45, Decay Heat Removal.

*J. *Waste Management and Disposal*—Report of ACRS subcommittee regarding DOE environmental assessments and NRC evaluation of proposed waste disposal repositories.

*K. *Systematic Review of Nuclear Power Plants*—Discuss proposed ACRS comments regarding the scope and timing of systematic reviews of nuclear power plants.

*L. *Future ACRS Activities*—Discuss anticipated ACRS activities and items proposed for review by the full Committee.

*M. *NRC Office of Research (tentative)*—Briefing regarding office activities by the Director, RES.

*N. *NRC Vendor Inspection Program (tentative)*—Briefing by representatives of NRC Staff regarding the NRC vendor inspection program.

March 7–9, 1985—Agenda to be announced.

April 11–13, 1985—Agenda to be announced.

Dated: January 16, 1985.

Samuel J. Chilk,

Secretary of the Commission.

[FR Doc. 85–1726 Filed 1–22–85; 8:45 am]

BILLING CODE 7590–01–M

[Docket No. 50–123]

Renewal of Facility Operating License; University of Missouri, Rolla

The U.S. Nuclear Regulatory Commission (the Commission) has issued Amendment No. 7 to Facility

Operating License No. R–79 for the University of Missouri (the licensee) which renews the license for operation of the training and research reactor located in Rolla, Missouri. The facility is a non-power reactor that has been operating at power levels not in excess of 200 kilowatts (thermal). The renewed Operating License No. R–79 will expire on November 20, 1989.

The amended license complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR, Chapter I. Those findings are set forth in the license amendment. Opportunity for hearing was afforded in the notice of the proposed issuance of this renewal in the **Federal Register** on May 9, 1980 at 45 FR 30752. No request for a hearing or petition for leave to intervene was filed following notice of the proposed action.

The Commission has prepared a Safety Evaluation Report (NUREG–1086) for the renewal of Facility Operating License No. R–79 and has, based on that report, concluded that the facility can continue to be operated by the licensee without endangering the health and safety of the public.

The Commission also has prepared an Environmental Assessment for the renewal of Facility Operating License No. R–79 dated November 16, 1984 and has concluded that this action will not have a significant effect on the quality of the human environment. The Notice of Finding of No Significant Environmental Impact was published in the **Federal Register** on January 10, 1985, at 50 FR 1285.

For further details with respect to this action, see (1) the application for amendment dated October 15, 1979, as supplemented, (2) the Finding of No Significant Environmental Impact, (3) Amendment No. 7 to Operating License No. R–79, (4) the Commission's related Safety Evaluation Report (NUREG–1086), and (5) Environmental Assessment. These items are available for public inspection at the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C. 20555.

Copies of NUREG–1086 may be purchased by calling (301) 492–9530 or by writing to the Publication Services Section, Division of Technical Information and Document Control, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, or purchased from the National Technical Information Service, Department of Commerce, 5285 Port Royal Road. Springfield, VA 22161.

Dated at Bethesda, Maryland, this 14th day of January 1985.

For the Nuclear Regulatory Commission.

Cecil O. Thomas,

Chief, Standardization & Special, Projects Branch, Division of Licensing.

[FR Doc. 85–1728 Filed 1–22–85; 8:45 am]

BILLING CODE 7590–01–M

SECURITIES AND EXCHANGE COMMISSION

[Release No. 23573; 70–7075]

Louisiana Power & Light Co. and Middle South Utilities, Inc.; Proposed Issuance and Sale of Common Stock by Subsidiary and Acquisition Thereof by the Holding Company

January 16, 1985.

Middle South Utilities, Inc. ("Middle South"), 225 Baronne Street, New Orleans, Louisiana 70112, a registered holding company, and its electric utility subsidiary company, Louisiana Power & Light Company ("LP&L"), 142 Delaronde Street, New Orleans, Louisiana 70174, have filed a proposal with this Commission pursuant to sections 6(a), 7, 9(a), and 10 of the Public Utility Holding Company Act of 1935 ("Act").

LP&L proposes to issue and sell from time to time through December 31, 1985, and Middle South proposes to acquire, an aggregate of not in excess of 15,152,000 additional shares of LP&L's authorized but unissued common stock, without nominal or par value. This amount includes 9,092,200 shares previously authorized to be issued and sold in 1984 which were not sold (HCAR No. 23271 (April 4, 1984)). The common stock will be sold at $6.60 per share for an aggregate cash purchase price of $100,000,000. LP&L will use the proceeds of such sales for the financing in part of (including the retirement of short-term indebtedness incurred in financing) its construction program (estimated to be $321,100,000 for the calendar year 1985) and for other corporate purposes.

The proposal and any amendments thereto are available for public inspection through the Commission's Office of Public Reference. Interested persons wishing to comment or request a hearing should submit their views in writing by February 11, 1985, to the Secretary, Securities and Exchange Commission, Washington, D.C. 20549, and serve a copy on the applicants at the addresses specified above. Proof of service (by affidavit or, in case of an attorney at law, by certificate) should be filed with the request. Any request for a hearing shall identify specifically the issues of fact or law that are disputed. A person who so requests will be notified of any hearing, if ordered, and will receive a copy of any notice or order issued in this matter. After said date, the proposal, as filed or as it may be amended, may be authorized.

For the Commission, by the Office of Public Utility Regulation, pursuant to delegated authority.

Shirley E. Hollis,

Assistant Secretary.

[FR Doc. 85–1664 Filed 1–22–85; 8:45 am]

BILLING CODE 8010–01–M

[Release No. 23572; 70–7074]

Mississippi Power & Light Co. and Middle South Utilities, Inc.; Proposed Issuance and Sale of Common Stock by Subsidiary and Acquisition Thereof by the Holding Company

January 16, 1985.

Middle South Utilities, Inc. ("Middle South"), 225 Baronne Street, New Orleans, Louisiana 70112, a registered holding company, and its electric utility subsidiary company, Mississippi Power & Light Company ("MP&L"), P.O. Box 1640, Jackson, Mississippi 39205, have filed a proposal with this Commission pursuant to sections 6(a), 7, 9(a), and 10 of the Public Utility Holding Company Act of 1935 ("Act").

MP&L proposes to issue and sell from time to time through December 31, 1985, and Middle South proposes to acquire, an aggregate of not in excess of 1,305,000 additional shares of MP&L's authorized but unissued common stock, without nominal or par value. This amount includes the 1,087,000 shares previously authorized to be issued and sold in 1984, none of which were sold (HCAR No. 23271 (April 4, 1984)). The common stock will be sold at $23.00 per share for an aggregate cash purchase price of $30,015,000. MP&L will use the proceeds of such sales for the payment in part of short-term borrowings, for the financing in part of its 1985 construction program (estimated to be $41,400,000), and for other corporate purposes.

The proposal and any amendments thereto are available for public inspection through the Commission's Office of Public Reference. Interested persons wishing to comment or request a hearing should submit their views in writing by February 11, 1985, to the Secretary, Securities and Exchange Commission, Washington, D.C. 20549, and serve a copy on the applicants at the addresses specified above. Proof of service (by affidavit or, in case of an attorney at law, by certificate) should be filed with the request. Any request for a

hearing shall identify specifically the issues of fact or law that are disputed. A person who so requests will be notified of any hearing, if ordered, and will receive a copy of any notice or order issued in this matter. After said date, the proposal, as filed or as it may be amended, may be authorized.

For the Commission, by the Office of Public Utility Regulation, pursuant to delegated authority.

Shirley E. Hollis,

Assistant Secretary.

[FR Doc. 85-1663 Filed 1-22-85; 8:45 am]

BILLING CODE 8010-01-M

[Release No. 14327; 812-5941]

Paine, Webber Municipal Bond Fund First Series and Subsequent Series, et al.; Application for an Order Exempting Certain Principal Transactions

January 16, 1985.

Notice is hereby given that Paine, Webber Municipal Bond Fund First Series and Subsequent Series, The Municipal Bond Fund, Series 1 through Series 43, The Municipal Bond Trust, Series 44 and Subsequent Series, The Municipal Bond Trust, Multi-State Program, Series 1 and Subsequent Series, The Municipal Bond Trust, Multiple Maturity Program, Series 1 and Subsequent Series, The Municipal Bond Trust, California Series A and Subsequent Series, The Municipal Bond Trust, Discount Series 1 and Subsequent Series, The Municipal Bond Trust, Insured Series 1 and Subsequent Series, all future series of the Municipal Bond Trust (said trusts collectively referred to as "Trusts") and PaineWebber Incorporated ("PaineWebber") (PaineWebber and Trusts collectively referred to as "Applicants"), 1221 Avenue of the Americas, New York, New York 10020, filed an application on September 21, 1984, and an amendment thereto on November 21, 1984, for an order of the Commission pursuant to sections 6(c) and 17(b) of the Investment Company Act of 1940 ("Act"), exempting certain principal transactions between the Trusts and PaineWebber from the provisions of section 17(a) of the Act in the manner and on the conditions set forth below. All interested persons are referred to the application on file with the Commission for a statement of the representations made therein, which are summarized below, and to the Act for the text of its relevant provisions.

The application states that the Trusts in the Multi-State Series consist of two or more separate unit investment trusts, and that all other Trusts consist of separate unit investment trusts, each created under the laws of New York by trust agreements or indentures among Paine Webber as sponsor ("Sponsor"), United States Trust Company of New York as trustee ("Trustee") and Standard & Poor's Corporation and Kenny Information Systems as evaluator. The investment objectives of the Trusts are the receipt of interest income exempt from federal income taxation and conservation of capital. Trusts in the California Series or Multi-State Series also have investment objectives of interest income exempt from state income taxation for residents in states for which the Trust is named. Units representing fractional undivided interests in each of the Paine, Webber Series, the National Series, the California Series, the Discount Series, the Multiple Maturity Series, the Insured Series and the Multi-State Series have been, and units for subsequent series will be, registered with the Commission under the Securities Act of 1933 prior to an offering by the Sponsor.

According to the application, purchasers of Trust units ("Certificateholders") receive interest and principal distributions, net of expenses and redemptions, representing their proportionate share of interest and priincipal received by the Trust. The Sponsor intends to maintain a market for Trust units and continously offer to purchase units at a price equal to the redemption price as described in the Trust's prospectus. The Sponsor, as a Certificateholder, may redeem units in its inventory, and if the Sponsor no longer maintains a secondary market, other Certificateholders may redeem units with the Trustee. If redemption demands exceed funds available, the Trusts have the power, pursuant to their respective Trust agreements, to sell portfolio bonds from a list of bonds designated by the Sponsor, or if a list is not maintained, by Trustee designation. Bonds are also sold to meet expenses in the same manner. Under specific circumstances enumerated in each Trust agreement, the Sponsor may direct the Trustee to sell bonds. Examples of instances triggering a bond sale include a default, or if the interest on a bond is deemed subject to Federal income taxation.

Trusts have two methods to effect bond sales: (1) The Trustee can approach several dealers and sell to the highest bidder, or (2) the Trustee can place an order to sell with one dealer (an "Introducing Dealer") who in turn retains a broker ("Clearing Broker") who communicates the availability of the bond by posting the offer on a wire system with contact to 300 to 400 dealers. The Clearing Broker culls the bids and selects the highest bidder, retaining a concession as does the Introducing Dealer. Applicants represent that the latter method has obtained more favorable prices to the Trusts because of the broader exposure to the bond offering by potential purchasers.

The application states that Clearing Brokers who have elected to operate under the net capital requirements of Rule 15c3-1(a) promulgated pursuant to the Securities Exchange Act of 1934 ("Exchange Act") may deal only with Introducing Dealers who are registered as broker-dealers under the Exchange Act. Since the Trustee is not a registered broker-dealer, it must retain an Introducing Dealer who is compensated for the minimal service of communicating orders and contacting the Clearing Broker. Purchasing for its own account, an Introducing Dealer acts as principal in transactions which section 17(a) of the Act, if applicable, prohibits as unlawful unless exempted by section 17(b) of the Act. PaineWebber is a municipal securities dealer who currently acts as an Introducing Dealer in connection with non-Trust bond sales. Applicants propose, and request an order of exemption, pursuant to section 6(c) and 17(b), to permit PaineWebber to purchase bonds from the Trusts as an Introducing Dealer for compensation less than the generally prevailing market rate (the "Transaction").

Applicants represent that the Transaction will benefit the Trusts and Certificateholders by reason that PaineWebber as the Introducing Dealer will provide the same service at less cost and subject to conditions which prevent any overreaching on the part of any person concerned. Applicants represent that PaineWebber is assured to receive the best price from the Clearing Broker because PaineWebber does not and will not influence the bids submitted by other dealers. Since the Trustee sells bonds only under limited and defined circumstances, PaineWebber cannot cause the Trusts to sell bonds merely to generate concessions. PaineWebber further represents that it will not cause the Trusts to sell bonds merely to generate fees; moreover, PaineWebber acknowledges that as a municipal securities dealer, it is subject to the rules of the Municipal Securities Rulemaking Board ("MSRB") which prohibit churning.

The application further states that the Transaction will safeguard Trust assets by reducing concession expense. Certificateholders' investment goals are long term oriented, according to the

Applicants, therefor it is advantageous for Certificateholders to have the maximum amount of funds invested as principal.

Applicants further acknowledge that PaineWebber , as the Introducing Dealer, and Clearing Broker, are subject to the rules of the Exchange Act and of the MSRB. Among the MSRB rules governing the Transaction are : (1) Maintenance of books and records, including customer account information, transaction information and record retention, (2) requirements as to the extension of credit, (3) fidelity bonding requirements, (4) confirmation requirements, (5) requirements to use reasonable efforts to obtain a fair and reasonable price relative to prevailing market conditions, and, (6) requirements to deal fairly with all persons and a correlative prohibition against deceptive, dishonest or unfair practices. Applicants have agreed to make available for ready inspection by the Commission all records required to be kept by the Applicants relating to the Transaction pursuant to the Exchange Act and the MSRB rules.

Applicants also contend that if the Transaction was effected as an agency transaction under the provisions of section 17(e) of the Act and Rule 17e–1 promulgated thereunder, the compensation paid to PaineWebber would be considered fair and reasonable when compared to fees received by others in connection with similar transactions. Applicants represent that PaineWebber's fees will always be less than that received by non-affiliated Introducing Dealers. To assure that PaineWebber receives a concession less than the prevailing market rate, the Trustee and PaineWebber will monitor the currently prevailing concessions charged by non-affiliated Introducing Dealers.

Applicants conclude that under the terms and conditions set forth herein, and as regulated under the Exchange Act and MSRB rules, PaineWebber will provide equal services to the Trusts at less cost than non-affiliated Introducing Dealers, that the terms of the Transaction, including the consideration to be paid or received, are reasonable and fair and do not involve overreaching on the part of any person concerned, that the Transaction is consistent with the policy of each registered investment company concerned, as recited in its registration statement and reports filed under the Act, and that the Transaction is consistent with the general policies of the Act.

Applicants also believe that the Transaction is appropriate in the public interest and consistent with the protection of investors and the purposes fairly intended by the Act.

Notice is further given that any interested person wishing to request a hearing on the application may, not later than February 11, 1985, at 5:30 p.m., do so by submitting a written request setting forth the nature of his/her interest, the reasons for the request, and the specific issues of fact or law that are disputed, to the Secretary, Securities and Exchange Commission, Washington, D.C. 20549. A copy of the request should be served personally or by mail upon Applicant at the address stated above. Proof of service (by affidavit or, in the case of an attorney-at-law, by certificate) shall be filed with the request. After said date, an order disposing of the application will be issued unless the Commission orders a hearing upon request or upon its own motion.

For the Commission, by the Division of Investment Management, pursuant to delegated authority.

Shirley E. Hollis,

Assistant Secretary.

[FR Doc. 85–1665 Filed 1–22–85; 8:45 am]

BILLING CODE 8010–01–M

SMALL BUSINESS ADMINISTRATION

[License No. 09/09–0354]

Cogeneration Capital Fund; Issuance of a Small Business Investment Company License

On November 7, 1984, a notice was published in the **Federal Register** (49 FR 44581) stating that an application has been filed by Cogeneration Capital Fund, with the Small Business Administration (SBA) pursuant to § 107.102 of the Regulations governing small business investment companies (13 CFR 107.102 (1984)) for a license as a small business investment company.

Interested parties were given until close of business December 7, 1984, to submit their comments to SBA. No comments were received.

Notice is hereby given that, pursuant to section 301(c) of the Small Business Investment Act of 1958, as amended, after having considered the application and all other pertinent information, SBA issued License No. 09/09–0354 on January 3, 1985, to Cogeneration Capital Fund to operate as a small business investment company.

(Catalog of Federal Domestic Assistance Program No. 59.011, Small Business Investment Companies)

Dated: January 16, 1985.

Robert G. Lineberry,

Deputy Associate Administrator for Investment.

[FR. Doc. 85–1717 Filed 1–22–85; 8:45 am]

BILLING CODE 8025–01–M

Region IX Advisory Council; California; Public Meeting

The U.S. Small Business Administration Region IX Advisory Council, located in the geographical area of San Francisco, California, will hold a public meeting at 10:00 a.m. Tuesday, February 19, 1985, 211 Main Street—5th Floor—Conference Room 543, San Francisco, California, to discuss such matters as may be presented by members, staff of the U.S. Small Business Administration, or others present.

For further information, write or call Lawrence J. Wodarski, District Director, U.S. Small Business Administration, 211 Main Street—4th Floor, San Francisco, California 94105, (415) 974–0642.

Jean M. Nowak,

Director of Advisory Councils.

January 16, 1984.

[FR. Doc. 85–1718 Filed 1–22–85; 8:45 am]

BILLING CODE 8025–01–M

DEPARTMENT OF TRANSPORTATION

Federal Aviation Administration

Advisory Circulars; Small Airplanes

AGENCY: Federal Aviation Administration (FAA), DOT.

ACTION: Publication of Advisory Circulars; Part 23 Airplanes.

SUMMARY: The purpose of this notice is to advise the public of advisory circulars issued by the Small Airplane Certification Directorate since July 1983. These advisory circulars (AC), listed below, relate to Part 3 of the Civil Air Regulations (CAR) and/or Part 23 of the Federal Aviation Regulations (FAR). They were issued to inform the aviation public of an acceptable means of showing compliance to the applicable regulations, but the material is neither mandatory nor regulatory in nature.

FOR FURTHER INFORMATION CONTACT: Mr. Joseph Snitkoff, Supervisor, Policy and Guidance Section, ACE–111, Aircraft Certification Division, Federal Aviation Administration, 601 East 12th Street, Kansas City, Missouri 64106; Commercial Telephone (816) 374–6941, or FTS 758–6941.

SUPPLEMENTARY INFORMATION:

Background

These advisory circulars were developed in response to the needs identified by the FAA Airframe Policy and Program Review Public Meeting held in Wichita, Kansas on June 8–9, 1983; to previously issued policy information; to service histories; and to a recommendation from the National Transportation Safety Board (NTSB).

Comments

Interested parties were given the opportunity to review and comment on each advisory circular during the proposal and development phases. Notices were published in the **Federal Register** (49 FR 31522, 8–7–84) to announce the availability of, and request written comments to, the draft advisory circular. Each comment and suggestion was reviewed and resolved. Appropriate comments were incorporated in the AC. Many of the recommended changes that were adopted corrected minor technical problems or clarified existing material.

Withdrawn

Two draft advisory circulars, AC 20.XX, Installation of Plastic Foam and Metallic Mesh in Fuel Tank, and AC 23–XX, Reciprocating Engine Induction Air Filters, were withdrawn after the notices appeard in the **Federal Register** (48 FR 28166 6–20–83). It has been determined that AC 20–XX would not be effective from a crashworthiness standpoint, could result in maintenance problems, would increase chances of fuel contamination, and would increase atomization of escaping fuel during crash impact. Draft AC 23–XX was withdrawn due to limited technical information in the AC for the design of induction air filters.

Distribution

The published advisory circulars are available upon request through the U.S. Department of Transportation, Subsequent Distribution Unit, M–494.3, Washington, D.C. 20596.

Advisory Circulars Published

Subject No.	Subject	Date signed
AC 20–118	Emergency evacuation demonstration from small airplanes.	7/12/83
AC 23–2	Flammability tests	8/20/84
AC 23.607–1	Self-locking nuts on bolts subject to rotation.	8/24/84
AC 23.683–1	Control system operation test	9/25/84
AC 23.729–1	Landing gear doors and retraction mechanism.	3/26/84
AC 23.807–1	Emergency exists in small airplanes.	9/7/83
AC 23.807–2	Doors between pilot's compartment and passenger cabin in small airplanes.	9/22/83
AC 23.807–3	Emergency exits openable from the outside for small airplanes.	1/20/84
AC 23.1011–1	Procedures for determining acceptable fuel/oil ratio as required by sector 23.1011(b).	11/14/83
AC 23.1305–1	Installation of fuel flowmeters in small airplanes with continuous-flow, fuel-injection reciprocating engines.	12/21/84

Advisory Circulars Withdrawn

Subject No.	Subject	Date withdrawn
AC 20–XX	Installation of plastic foam and metallic mesh in fuel tank.	12/7/84
AC 23–XX	Reciprocating engine induction air filters.	12/2/83

Barry D. Clements,

Manager, Aircraft Certification Division.

[FR Doc. 85–1549 Filed 1–22–85; 8:45 am]

BILLING CODE 4910–13–M

Sunshine Act Meetings

Federal Register
Vol. 50, No. 15
Wednesday, January 23, 1985

This section of the FEDERAL REGISTER contains notices of meetings published under the "Government in the Sunshine Act" (Pub. L. 94-409) 5 U.S.C. 552b(e)(3).

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Consumer Product Safety Commission	1, 2
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1

CONSUMER PRODUCT SAFETY COMMISSION

Commission Meeting

TIME AND DATE: 9:30 a.m., Tuesday, January 22, 1985.

LOCATION: 810 Conference Room, 1111 18th Street, NW., Washington, D.C.

STATUS: Closed to the public.

MATTERS TO BE CONSIDERED:

Commission Procedures Review:

The Commission and staff will review internal procedures relating to Commission decisionmaking.

The Commission decided that agency business required scheduling this meeting without the normal notice.

For a recorded message containing the latest agenda information, call: 301-492-5709.

CONTACT PERSON FOR ADDITIONAL INFORMATION: Sheldon D. Butts, Office of the Secretary, 5401 Westbard Ave., Bethesda, Md. 20207, 301-492-6800.

Sheldon D. Butts,

Deputy Secretary.

January 18, 1985.

[FR Doc. 85-1780 Filed 1-18-85; 1:26 pm]

BILLING CODE 6355-01-M

2

CONSUMER PRODUCT SAFETY COMMISSION

Commission Meeting

TIME AND DATE: 9:30 a.m., Wednesday, January 23, 1985.

LOCATION: Third Floor Hearing Room, 1111 18th Street NW., Washington, D.C.

STATUS: Open to the public.

MATTERS TO BE CONSIDERED:

1. *TAB Report/Recommendations*
The staff will brief the Commission on public comments on the Toxicological Advisory Board's final report and will make recommendations with respect to implementing the Board's recommendations.
2. *Lawn Mower Blade Hand Guard Petition, CP 84-1*
The staff will brief the Commission on a petition from Todd Kent Campbell requesting the Commission to establish a rule under the Consumer Product Safety Act to require hand guards on rotary lawn mower blades when they are shipped for consumer use.

Closed to the public:

3. *OS #5372*
The Commission will consider issues related to OS #5372.
4. *Enforcement Matter OS #5043*
The Commission will consider Enforcement Matter OS #5043.

For a recorded message containing the latest agenda information, call: 301-492-5709.

CONTACT PERSON FOR ADDITIONAL INFORMATION: Sheldon D. Butts, Office of the Secretary, 5401 Westbard Ave., Bethesda, Md. 20207 301-492-6800.

Sheldon D. Butts,

Deputy Secretary.

January 18, 1985.

[FR Doc. 85-1779 Filed 1-18-85; 1:26 pm]

BILLING CODE 6355-01-M

3

EQUAL EMPLOYMENT OPPORTUNITY COMMISSION

DATE AND TIME: 2:00 p.m. (eastern time), Monday, January 28, 1985.

PLACE: Clarence M. Mitchell, Jr., Conference Room No. 200-C on the 2nd Floor of the Columbia Plaza Office Building, 2401 "E" Street, NW., Washington, DC 20507.

STATUS: Closed to the public.

MATTER TO BE CONSIDERED: *Closed:* Litigation Authorization; General Counsel Recommendations.

Note.—Any matter not discussed or concluded may be carried over to a later meeting. (In addition to publishing notices on EEOC Commission Meetings in the Federal Register, the Commission also provides a recorded announcement a full week in advance on future Commission sessions. Please telephone (202) 634-6748.)

Dated: January 18, 1985.

Cynthia C. Matthews,

Executive Officer.

[FR Doc. 85-1815 Filed 1-18-85; 3:02 pm]

BILLING CODE 6570-06-M

4

EQUAL EMPLOYMENT OPPORTUNITY COMMISSION

DATE AND TIME: 9:30 a.m. (eastern time), Tuesday, January 29, 1985.

PLACE: Clarence M. Mitchell, Jr., Conference Room No. 200-C, 2nd Floor, Columbia Plaza Office Building, 2401 "E" Street, NW., Washington, D.C. 20507.

STATUS: Part will be open to the public and part will be closed to the public.

MATTERS TO BE CONSIDERED:

1. Announcement of Notation Vote(s).
2. A Report on Commission operations (Optional).
3. New Privacy Act System for Claims Collection Records.
4. Policy Statement on Remedies and Relief for Individual Cases of Unlawful Discrimination.
5. Final Regulation Implementing section 4(g) of the ADEA 29 U.S.C. 623(g).

Closed:

Litigation Authorization, General Counsel Recommendations.

Note.—Any matter not discussed or concluded may be carried over to a later meeting. (In addition to publishing notices on EEOC Commission Meetings in the Federal Register, the Commission also provides a recorded announcement a full week in advance on future Commission sessions. Please telephone (202) 634-6748.)

Dated: January 18, 1985.

Cynthia C. Matthews,

Executive Officer.

[FR Doc. 85-1816 Filed 1-18-85; 8:45 am]

BILLING CODE 6570-06-M

5

FEDERAL DEPOSIT INSURANCE CORPORATION

Agency Meeting

Pursuant to the provisions of the "Government in the Sunshine Act" (5 U.S.C. 552b), notice is hereby given that the Federal Deposit Insurance Corporation's Board of Directors will meet in open session at 11:00 a.m. on Friday, January 25, 1985, to consider the following matters:

Summary Agenda: No substantive discussion of the following items is anticipated. These matters will be resolved with a single vote unless a member of the Board of Directors requests that an item be moved to the discussion agenda.

Disposition of minutes of previous meetings.

Application for consent to transfer assets in consideration of the assumption of deposit liabilities:

Bank of Indiana, National Association, Gary, Indiana, for consent to transfer certain assets to Bank of Indiana, FSB, Gary, Indiana, a non-FDIC-insured institution in organization, in consideration of the assumption of the liability to pay deposits made in Bank of indiana, National Association.

Application for consent to interchange and redesignate the main office and an existing branch:

County Bank of Merced, Merced, California, for consent to interchange and redesignate the present main office located at 490 West Olive Avenue, Merced, California, as the West Olive Branch and the Atwater Branch located at 735 Bellevue Road, Atwater, California, as the main office.

Application for consent to convert into a non-FDIC-insured institution:

Union Bank of Florida, Lauderhill, Florida.

Recommendation regarding the liquidation of a bank's assets acquired by the Corporation in its capacity as receiver, liquidator, or liquidating agent of those assets:

Memorandum and Resolution re: City and County Bank of Knox County, Knoxville, Tennessee

Memorandum and resolution re: Proposed amendment to Part 333 of the Corporation's rules and regulations, entitled "Extension of Corporate Powers," which would permit insured nonmember banks to offer and administer, with certain limitations, self-directed Individual Retirement and Keogh Plan accounts.

Reports of committees and officers:

Minutes of actions approved by the standing committees of the Corporation pursuant to authority delegated by the Board of Directors.

Reports of the Division of Bank Supervision with respect to applications, requests, or actions involving administrative enforcement proceedings approved by the Director or an Associate Director of the Division of Bank Supervision and the various Regional Directors pursuant to authority delegated by the Board of Directors.

Reports of the Director, Office of Corporate Audits and Internal Investigations:

Summary Audit Report re: Bank of Hackleburg, Hackleburg, Alabama, AP-367 (Memo dated December 3, 1984)

Summary Audit Report re: Atkinson Trust & Savings Bank, Atkinson, Illinois, Sr-449 (Memo dated December 3, 1984)

Summary Audit Report re: Watauga Valley Bank, Elizabethton, Tennessee, AP-379 (Memo dated December 31, 1984)

Summary Audit Report re: Security National Bank of Lubbock, Lubbock, Texas, NR-468 (Memo dated December 31, 1984)

Summary Audit Report re: First Security Bank, Erwin, Tennessee, AP-1984) (Memo dated December 31, 1984)

Summary Audit Report re: Deposit Insurance Transfer Agreement (Memo dated December 14, 1984)

Summary Audit Report re: Travel Voucher Claims (Memo dated December 20, 1984)

Summary Audit Report re: Processing of Payroll Changes and Savings Bonds (Memo dated December 21, 1984)

Summary Audit Report re: Decimus Asset Management System-Midwest Regional Office Audit (Memo dated December 28, 1984)

Memorandum re: Analysis of Results of 49 Liquidation Site Audits

Discussion Agenda:

No matters scheduled.

The meeting will be held in the Board Room on the sixth floor of the FDIC Building located at 550 17th Street, NW., Washington, D.C.

Requests for further information concerning the meeting may be directed to Mr. Hoyle L. Robinson, Executive Secretary of the Corporation, at (202) 389-4425.

Dated: January 18, 1985.

Federal Deposit Insurance Corporation.

Hoyle L. Robinson,

Executive Secretary.

[FR Doc. 85-1813 Filed 1-18-85; 3:01 pm]

BILLING CODE 6714-01-M

6

FEDERAL DEPOSIT INSURANCE CORPORATION

Agency Meeting

Pursuant to the provisions of the "Government in the Sunshine Act" (5 U.S.C. 552b), notice is hereby given that at 11:30 a.m. on Friday, January 25, 1985, the Federal Deposit Insurance Corporation's Board of Directors will meet in closed session, by vote of the Board of Directors, pursuant to sections 552b(c)(2), (c)(4), (c)(6), (c)(8), (c)(9) (A) (ii), and (c)(10) of Title 5, United States Code, to consider the following matters:

Summary Agenda: No substantive discussion of the following items is anticipated. These matters will be resolved with a single vote unless a member of the Board of Directors requests that an item be moved to the discussion agenda.

Recommendations with respect to the initiation, termination, or conduct of administrative enforcement proceedings (cease-and-desist proceedings, termination-of-insurance proceedings, suspension or removal proceedings, or assessment of civil money penalties) against certain insured banks or officers, directors, employees, agents or other persons participating in the conduct of the affairs thereof:

Names of persons and names and locations of banks authorized to be exempt from disclosure pursuant to the provisions of subsections (c)(6), (c)(8), and (c)(9)(A)(ii) of the "Government in the Sunshine Act" (5 U.S.C. 552b (c)(6), (c)(8), and (c)(9)(A)(ii)).

Note.—Some matters falling within this category may be placed on the discussion agenda without further public notice if it becomes likely that substantive discussion of those matters will occur at the meeting.

Discussion Agenda:

Applications pursuant to section 19 of the Federal Deposit Insurance Act for consent to service of a person convicted of an offense involving dishonesty or a breach of trust as a director, officer, or employee of an insured bank:

Names of persons and name and location of bank authorized to be exempt from disclosure pursuant to the provisions of subsections (c)(6), (c)(8), and (c)(9) (A)(ii) of the "Government in the Sunshine Act" (5 U.S.C. 552b(c)(6), (c)(8), and (c)(9) (A)(ii)).

Application for consent to transfer assets in consideration of the assumption of deposit liabilities:

Citizens Bank of Weirton, Weirton, West Virginia, an insured State nonmember bank, for consent to transfer certain assets to Fed One, F.A., Wheeling, West Virginia, a non-FDIC-insured institution, in consideration of the assumption of the liability to pay deposits made in Citizens Bank of Weirton, Weirton, West Virginia.

Recommendation regarding the liquidation of a bank's assests acquired by the Corporation in its capacity as receiver, liquidator, or liquidating agent of those assets:

Case No. 46,159 Reserves for Losses, 230 Open Liquidation Cases

Personnel actions regarding appointments, promotions, administrative pay increases, reassignments, retirements, separations, removals, etc.:

Names of employees authorized to be exempt from disclosure pursuant to the provisions of subsections (c)(2) and (c)(6) of the "Government in the Sunshine Act" (5 U.S.C. 552b(c)(2) and (c)(6)).

The meeting will be held in the Board Room on the sixth floor of the FDIC Building located at 550 17th Street, NW., Washington, D.C.

Requests for further information concerning the meeting may be directed to Mr. Hoyle L. Robinson, Executive Secretary of the Corporation, at (202) 389–4425.

Dated: January 18, 1985.

Federal Deposit Insurance Corporation.

Hoyle L. Robinson,

Executive Secretary.

[FR Doc. 85–1814 Filed 1–18–85; 3:02 pm]

BILLING CODE 6714–01–M

7

FEDERAL ENERGY REGULATORY COMMISSION

January 17, 1985

TIME AND DATE: 10:00 a.m., January 24, 1985.

PLACE: Room 9306, 825 North Capitol Street, NE., Washington, D.C. 20426.

STATUS: Open.

MATTERS TO BE CONSIDERED: Agenda.

Note.—Items listed on the agenda may be deleted without further notice.

CONTRACT PERSON FOR MORE INFORMATION: Kenneth F. Plumb, Secretary. Telephone (202) 357–8400.

This is a list of matters to be considered by the Commission. It does not include a listing of all papers relevant to the items on the agenda; however, all public document may be examined in the Division of Public Information.

Consent Power Agenda—608th Meeting, January 24, 1985, Regular Meeting (10:00 a.m.)

CAP–1. Project No. 8450–000, Small Hydro East
CAP–2. Project No. 3268–002, Griswold Textile Print, Inc.
CAP–3. Project No. 7049–003, Foundry Associates
CAP–4. Project No. 5677–004, Swanson Mining Corp.
CAP–5. Project No. 6441–002, South Fork Hydroelectric Association
CAP–6. Project No. 4186–002, Stowe Mills, Inc.
CAP–7. Project No. 7809–001, Emerson Falls Hydro Associates
CAP–8. Docket No. OF83–425–003, Electrodyne Research Corp.
CAP–9. Docket No. ER82–769–005, Minnesota Power & Light Co.
CAP–10. Docket No. ER84–654–001, Yankee Atomic Electric Co.
CAP–11. Docket No. ER85–184–000, Carolina Power & Light Co.
CAP–12. Docket No. ER82–123–000, Kansas City Power & Light Co.
CAP–13. Docket No. ER84–554–000, Holyoke Water Power Co. and Holyoke Electric Power Co.
CAP–14. Docket No. OF85–22–000, Bethlehem Steel Corp., Burns Harbor No. 2
CAP–15. Docket No. OF85–21–000, Bethlehem Steel Corp., Burns Harbor No. 2

Consent Miscellaneous Agenda

CAM–1 Omitted.
CAM–2. Docket No. FA84–3–000, Puget Sound Power & Light Co.
CAM–3. Docket No. RO–84–6–000, Gulf Oil Corp.
CAG–1. Docket No. RP85–19–001, Trunkline Gas Co.; Docket No. RP85–20–001, Panhandle Eastern Pipe Line Co.
CAG–2. Docket No. RP85–58–000, El Paso Natural Gas Co.
CAG–3. Docket No. RP85–59–000, National Fuel Gas Supply Corp.
CAG–4. Docket No. RP85–60–000, Overthrust Pipeline Co.
CAG–5. Docket Nos. TA85–1–16–000 and 001 (PGA85–1), National Fuel Gas Supply Corp.
CAG–6. Docket Nos. TA85–1–18–000 and 001, Texas Gas Transmission Corp.
CAG–7. Docket Nos. TA85–1–61–000 and 001, Bayou Interstate Pipeline System
CAG–8. Docket Nos. TA85–2–17–000 and 001, Texas Eastern Transmission Corp.
CAG–9. Docket No. RP82–54–016, Colorado Interstate Gas Co.
CAG–10. Docket No. RP82–54–015, Colorado Interstate Gas Co.
CAG–11. Docket Nos. RP82–125–012 and 013, Tennessee Gas Pipeline Co., a Division of Tenneco Inc.
CAG–12. Docket Nos. TA85–1–29–002, 003 and 004, Transcontinental Gas Pipe Line Corp.
CAG–13. Docket Nos. TA85–1–37–002, 003, TA85–2–37–003 and RP85–1–002, Northwest Pipeline Corp.
CAG–14. Docket Nos. TA85–1–47–002 and 003, MIGC, Inc.
CAG–15. Docket No. RP83–6–001, Columbia Gas Transmission Corp. v. Tennessee Gas Pipeline Co., a Division of Tenneco Inc.; Docket No. RP–83–19–000, Tennessee Gas Pipeline Co., a Division of Tenneco Inc. v. Columbia Gas Transmission Corp.; Docket No. RP83–10–000, the Inland Gas Co., Inc. v. Tennessee Gas Pipeline Co., a Division of Tenneco. Inc.; Docket No. RP83–20–000, Tennessee Gas Pipeline Co., a Division of Tenneco Inc. v. The Inland Gas Co., Inc.; Docket No. RP84–17–000, Tennessee Gas Pipeline Co., a Division of Tenneco Inc.
CAG–16. Docket No. RP78–66–000, Cimarron Transmission Co.
CAG–17. Docket Nos. TA85–1–46–000 and 001, Kentucky West Virginia Gas Co.
CAG–18. Docket Nos. TA85–1–48–000 and 001, 002, RP75–96–000 and RP76–100–000, ANR Pipeline Co.
CAG–19. Docket No. RP85–18–000, Natural Gas Pipeline Co. of America
CAG–20. Docket Nos. RP84–107–000 and RP84–137–000, Arkansas Louisiana Gas Co.
CAG–21. Docket Nos. ST84–54–000, 001, ST83–257–000, 001, ST84–630–000 and 001, Delhi Gas Pipeline Corp.
CAG–22. Docket No. ST83–273–001, Delhi Gas Pipeline Corp.
CAG–23. Docket Nos. ST83–265–000, 001, ST82–76–000 and 001, Producer's Gas Co.
CAG–24. Docket No. ST84–871–000, IMC Pipeline Co., Inc.
CAG–25. Docket No. RI84–6–000, Texas Production Co., FERC Gas Rate Schedule No. 1; Docket No. RI84–7–000, Pinto, Inc., FERC Gas Rate Schedule No. 1; Docket No. RI84–8–000, ECEE, Inc., FERC Gas Rate Schedule No. 1
CAG–26. Docket Nos. RI74–188–047 and RI75–21–042, Independent Oil & Gas Association of West Virginia
CAG–27. Docket No. CI80–106–000, Shell Oil Co.
CAG–28. Omitted.
CAG–29. Docket No. CP83–452–016, Columbia Gas Transmission Corp. and Columbia Gulf Transmission Co.
CAG–30. Docket Nos. CP74–138–010, CP83–433–000, RP81–85–000, 003, RP83–93–000, 003 and FA85–01–000, Trunkline LNG Co.; Docket Nos. CP83–75–000 and TA80–2–22–003, Consolidated System LNG Co.; Docket Nos. CP83–75–000, TA80–2–21–002 and 003, Columbia LNG Corp.; Docket Nos. CP83–75–000, RP80–136–000 and 003, Southern Energy Co.
CAG–31. Omitted.
CAG–32. Docket No. CP85–130–000, Phillips Gas Pipeline Co.
CAG–33. Docket No. CP84–525–000, K N Energy, Inc.; Docket Nos. CI84–466–000, CI84–467–000, CI84–468–000, CI84–469–000, CI84–470–000, CI84–471–000, CI84–472–000, CI84–473–000 and CI84–474–000, Plains Production Co.
CAG–34. Docket No. CP83–420–000, Northern Natural Gas Co., Division of Internorth, Inc.
CAG–35. Docket No. CP84–71–000, Lawrenceburg Gas Transmission Corp.
CAG–36. Docket No. CP85–41–000, American Petrofina Co. of Texas and Petrofina Delaware, Inc.
CAG–37. Docket No. CI–85–50–000, Diamond Shamrock Exploration Co.
CAG–38. Docket No. CI85–99–000, Union Texas Petroleum Corp.

I. Licensed Project Matters

P–1. Procedure for assessing hydropower projects clustered in river basins.
P–2. Project Nos. 2516–003 and 004, Potomac Edison Co.
P–3. Project No. 8429–003, Aliceville Hydro Associates

II. Electric Rate Matters

ER–1. Omitted.
ER–2. Omitted.
ER–3. Omitted.
ER–4. Docket No. ID–2144–000, William S. Lee
ER–5. Omitted.
ER–6. Docket Nos. QF84–73–000, QF84–74–000 and QF84–75–000, Turbo Gas and Electric, Ltd.
ER–7. Docket No. QF84–434–000, Luz Solar Partners Ltd., et al.

Miscellaneous Agenda

M–1. Docket No. RM84–16–003, methodology for sales of electric power to the Bonneville Power Administration
M–2. Reserved.
M–3. Reserved.
M–4. Docket Nos. RM80–8–001, 002, 003, 004 and 005, bona fide offers; right of first refusal
M–5. Omitted.

I. Pipeline Rate Matters

RP–1. Docket Nos. RP80–136–000 and 004, Southern Natural Gas Co.

RP–2. Docket Nos. RP83–35–000, RP81–109–000, RP82–37–000, RP74–41–016, Texas Eastern Transmission Corp.

Producer Matters

CI–1. Omitted.
CI–2. Omitted.
CI–3. Omitted.
CI–4. (a) Docket No. CI78–704–002, Mitchell Energy Corp.; (b) Docket No. G–3653–007, et al., Sun Exploration and Production Co., et al.; Docket No. G–3711–006, et al., Breton Resources Co., et al.; Docket Nos. CI83–337–003 and CI83–350–003, Exxon Corp.

III. Pipeline Certificate Matters

CP–1. Docket No. CP83–14–047, Northern Natural Gas Co., a Division of Internorth, Inc.

Kenneth F. Plumb,

Secretary.

[FR Doc. 85–1741 Filed 1–18–85; 10:04 am]

BILLING CODE 6717–01–M

8

LEGAL SERVICES CORPORATION BOARD OF DIRECTORS MEETING

"FEDERAL REGISTER" CITATION OF PREVIOUS ANNOUNCEMENT: 50 FR 2371.

CHANGE IN THE MEETING: The following agenda item has been added to the list of agenda items scheduled for consideration at the January 25, 1985, meeting:

Agenda Item 6. Reconsideration of Line Item Allocations of FY 1986 Budget Mark

CONTACT PERSON FOR MORE INFORMATION: Thomas J. Opsut, Executive Office, (202) 272–4040.

Dated: January 18, 1985.

Donald P. Bogard,

President.

[FR Doc. 85–1744 Filed 1–18–85; 10:48 am]

BILLING CODE 6820–35–M

9

PAROLE COMMISSION

[5PO401]

Public Announcement

DATE AND TIME: Thursday, January 31, 1985—2:30 p.m. to 6:00 p.m.

PLACE: The Holiday Inn, 500 E First Street, Long Beach, California.

STATUS: Closed pursuant to a vote to be taken at the beginning of the meeting.

MATTERS TO BE CONSIDERED: Appeals to the Commission of approximately 20 cases decided by the National Commissioners pursuant to a reference under 28 CFR 2.17 and appealed pursuant to 28 CFR 2.27. These are all cases originally heard by examiner panels wherein inmates of Federal prisons have applied for parole or are contesting revocation of parole or mandatory release.

CONTACT PERSON FOR MORE INFORMATION: Linda Wines Marble, Chief Analyst, National Appeal Board, United States Parole Commission, (301) 492–5987.

Dated: January 18, 1985.

Joseph A. Barry,

General Counsel, United States Parole Commission.

[FR Doc. 85–1782 Filed 1–18–85; 1:26 pm]

BILLING CODE 4410–01–M

10

PAROLE COMMISSION

[5P0401]

Public Announcement

PLACE: The Holiday Inn, 500 E. First Street, Long Beach, California.

DATE AND TIME:

Friday, February 1, 1985—9:00 a.m. to 5:30 p.m.

Saturday, February 2, 1985—9:00 a.m. to 12:00 noon.

STATUS: Open.

MATTERS TO BE CONSIDERED:

1. Approval of minutes of open business meeting of October 23–25, 1984.
2. Reports from the Chairman, Vice Chairman, Commissioners, Legal, Research, Case Operations, and the Administrative Sections.
3. Probation Officers carrying firearms.
4. Community participation in parole decision-making.
5. F–3 Reports re Committed Fines—propossed contents of the reports.
6. Presentation by Barbara Meierhoefer of the Federal Judicial Center.
7. Payment of child support and alimony as a condition of parole.
8. Progress Report on Community Service project.

Consent Agenda

The following Consent Agenda Items shall be deemed adopted by consent and will not be discussed at the meeting unless a request to discuss a particular item has been received by January 28, 1985:

9. Change in 28 CFR 2.40 defining "criminal records" as one or more felony convictions.
10. R&P Memo # 1 (dated November 5, 1984) previously distributed to the Commissioners.

CONTACT PERSON FOR MORE INFORMATION: Peter B. Hoffman, Director of Research, United States Parole Commission, (301) 492–5980.

Dated: January 18, 1985.

Joseph A. Barry,

General Counsel, United States Parole Commission.

[FR. Doc. 85–1781 Filed 1–18–85; 1:26 pm]

BILLING CODE 4410–01–M

11

SECURITIES AND EXCHANGE COMMISSION

"FEDERAL REGISTER" CITATION OF PREVIOUS ANNOUNCEMENT: 50 CFR 19749, January 14, 1985.

STATUS: Closed meeting.

PLACE: 1450 Fifth Street, NW., Washington, D.C.

DATE PREVIOUSLY ANNOUNCED: Tuesday, January 8, 1985.

CHANGE IN THE MEETING: Additional item. The following item was considered at a closed meeting scheduled for Tuesday, January 15, 1985, at 10:00 a.m.:

Settlement of injunctive action.

Chairman Shad and Commissioners Treadway, Cox and Marinaccio determined that Commission business required the above change and that no earlier notice thereof was possible.

At time changes in Commission priorities require alterations in the scheduling of meeting items. For further information and to ascertain what, if any, matters have been added, deleted or postponed, please contact: Steve Molinari at (202) 272–2467

John Wheeler,

Secretary.

January 18, 1984.,

[FR Doc. 85–1787 Filed 1–21–85; 1:46 pm]

BILLING CODE 8010–01–M

12

SECURITIES AND EXCHANGE COMMISSION

Notice is hereby given, pursuant to the provisions of the Government in the Sunshine Act, Pub. L. 94–409, that the Securities and Exchange Commission will hold the following meetings during the week of January 12, 1985, at 450 Fifth Street, NW., Washington, D.C.

An open meeting will be held on Tuesday, January 22, 1985, at 10:00 a.m, in Room 1C30 followed by a closed meeting.

The Commissioners, Counsel to the Commissioners, the Secretary of the Commission, and recording secretaries will attend the closed meeting. Certain staff members who are responsible for the calendared matters may be present.

The General Counsel of the Commission, or his designee, has certified that, in his opinion, the items to be considered at the closed meeting may be considered pursuant to one or more of the exemptions set forth in 5 U.S.C. 552b(c) (4), (8), (9)(A) and (10) and 17 CFR 200.402(a)(4), (8), (9)(i) and (10).

Chairman Shad and Commissioners Treadway, Cox and Marinaccio voted to consider the items listed for the closed meeting in closed session.

The subject matter of the open meeting scheduled for Tuesday, January 22, 1985, at 10:00 a.m., will be:

1. Consideration of whether to grant the applications filed by Robert E. Lee and Peter F. Faletti seeking exemption relief from the prohibitions of Section 9 of the Investment Company Act of 1940. For further information, please contact Jerry A. Isenberg at (202) 272–2976.

2. Consideration of whether to issue an order authorizing Central and South West Financial, Inc., a nonutility subsidiary company of Central and South West Corporation, a registered holding company, to enter into leveraged leases for the purpose of reducing forecasted consolidated income tax liability. For further information, please contact William C. Weeden at (202) 272–7699.

The subject matter of the closed meeting scheduled for Tuesday, January 22, 1985, following the 10:00 a.m. open meeting, will be:

Formal orders of investigation.
Institution of administrative proceedings of an enforcement nature.

At times changes in Commission priorities require alterations in the scheduling of meeting items. For further information and to ascertain what, if any, matters have been added, deleted or postponed, please contact: Barry Mehlman (202) 272–2648.

John Wheeler,

Secretary.

January 18, 1985.

[FR Doc. 85–1794 Filed 1–18–85; 8:45 am]

BILLING CODE 8010–01–M

13

SYNTHETIC FUELS CORPORATION

Meeting of the Comprehensive Strategy Committee of the Board of Directors

ACTION: Notice of meeting.

SUMMARY: Interested members of the public are invited to attend and observe a meeting of the Comprehensive Strategy Committee of the Board of Directors of the United States Synthetic Fuels Corporation to be held at the time, date and place specified below by telephone conference call. This public announcement is made pursuant to the open meeting requirements of section 116(f)(1) of the Energy Security Act (94 Stat. 611, 637; 42 U.S.C. 8701, 8712(f)(1) and section 4 of the Corporation's Statement of Policy on Public Access to Board meetings. During the meeting, the Board of Directors may consider a resolution to close a portion of the meeting pursuant to Article II, section 4 of the Corporation's By-laws, and section 116(f) of the said Act.

MATTER TO BE CONSIDERED: Discussion of Draft of "Resource-Technology Combinations Proposed for SFC Business Plan."

TIME AND DATE: 12:00 p.m., January 24, 1985.

PLACE: U.S. Synthetic Fuels Corporation, 2121 K Street, NW., Room 503, Washington, D.C. 20586.

PERSON TO CONTACT FOR MORE INFORMATION: If you have any questions regarding this meeting, please contact Mr. Owen J. Malone, Assistant Secretary, at (202) 822–6341.

United States Synthetic Fuels Corporation.

Leonard Rawicz,

Acting General Counsel.

January 18, 1985.

[FR Doc. 85–1765 Filed 1–18–85; 12:07 pm]

BILLING CODE 0000–00–M

federal register

Wednesday
January 23, 1985

Part II

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 600, 610, and 680
Biological Products; Allergenic Extracts; Implementation of Efficacy Review; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 600, 610, and 680

[Docket No. 81N-0096]

Biological Products; Allergenic Extracts; Implementation of Efficacy Review

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations in response to the report and recommendations of the Panel on Review of Allergenic Extracts (the Panal). The Panel reviewed the safety, efficacy, and labeling of allergenic extract products and related licensed biological products. Generally referred to as allergenic extracts, these products are defined under § 680.1(a) (21 CFR 680.1(a)). They are produced from allergenic source materials such as pollens, molds, foods, house dust and other miscellaneous inhalants, insects, and mammalian and avian epidermis. On the basis of the Panel's findings and recommendations, FDA is proposing to classify those products in Category I (safe, effective, and not misbranded) and Category IIIA (to remain licensed pending reclassification into either Category I or Category II) and is inviting comments and the submission of additional data on the status of these products.

FDA is also announcing its conclusions as to those products which are in Category II (unsafe, ineffective, or misbranded) and Category IIIB (licenses to be revoked pending completion of studies permitting determinations of effectiveness and safety). In the near future, FDA will publish a notice of opportunity for hearing (NOH) to revoke the manufacturer's approval under their licenses to produce products in Category IIIB. Comments and additional data will be requested in the NOH..

DATES: Comments on the classification of products into Category I and IIIA and on proposed amendments to the biologics regulations should be submitted by April 23, 1985. Comments on the confidentiality of data submitted for review by the Panel should by submitted by February 22, 1985. FDA proposes that any final regulation based on this proposal become effective 180 days after the date the final regulation is published in the **Federal Register**.

Labeling requirements, other than prominent statements required for products proposed only for use in diagnosis, would be effective 30 months after publication of the final regulation but, consistent with the existing provisions under § 201.59 (21 CFR 201.59), revised labeling would be due to the submitted to the Office of Biologics Research and Review (OBRR), Center for Drugs and Biologics, by 6 months after publication of the final regulation.

Amendments to a license application, other than labeling amendments, would be required to be submitted to FDA within 180 days after the date a final rule is published in the **Federal Register**. For products recommended generically for Category I of Category IIIA for diagnosis but Category IIIB for immunotherapy, the prominent statements required on the package label and package insert would become effective 180 days after the date of publication in the **Federal Register** of a notice of opportunity for hearing.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMAITON CONTACT: About this proposal: Michael L. Hooton, Center for Drugs and Biologics (HFN-368), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1306.

About labeling requirements and changes in biological licenses; Michael G. Beatrice, Center for Drugs and Biologics (HFN-825), Food and Drug Adminstration, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-5433.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of February 13, 1973 (38 FR 4319), the Commissioner of Food and Drugs issued § 601.25 (21 CFR 601.25) concerning procedures for the review of the safety, effectiveness, and labeling of biological products licensed prior to July 1, 1972. Under a redesignation of panel assignments published in the **Federal Register** of June 19, 1974, (39 FR 21176), the biological products reviewed were assigned to one of the following categories: (a) bacterial vaccines and bacterial antigens with "no U.S. standard of potency," (b) bacterial vaccines and toxoids with standards of potency, (c) viral vaccines and rickettsial vaccines, (d) allergenic extracts, (e) skin test antigens, or (f) blood and blood derivatives.

Under § 601.25, FDA assigned respnsiblity for the initial review of each of the biological product categories to a separate independent advisory review panel consisting of qualified experts to ensure objectivity of the review and public confidence in the use of these products. Each panel was charged with preparing an advisory report to the agency which was to: (1) evaluate the safety and effectiveness of the biological product, (2) review the labeling of the biological product, and (3) advise FDA on which biological products under review are safe, effective, and not misbranded. The advisory report includes a statement classifying products into one of three categories.

Category I designates those biological products determined by the Panel to be safe, effective, and not misbranded. Category II designates those biological products determined by the Panel to be unsafe or ineffective or to be misbranded. Category III designates those biological products for which further testing is required because the available data are insufficient for classification. those bilogical products in Category III for which continued licensing, manufacturing, and marketing are recommended are designated as Category IIIA. Those biological products in Category III for which the suspension of the manufacturers' approval to produce the products under their licenses is recommended are designated as Category IIIB.

The definition above of Category IIIA applied at the time of the Panel's review and served as a basis for the Panel's recommendations. In the **Federal Register** of October 5, 1982 (47 FR 44062), FDA revised § 601.25 and established new § 601.26 (21 CFR 601.26) to provide for the review and reclassification by an advisory review committee of products currently in Category IIIA. The purpose of the review would be to reclassify each Category IIIA product into either Category I or Category II.

The effectiveness of all Category IIIA allergenic extracts will be determined as part of the reclassification process. The advisory review committee involved in the reclassification of Category IIIA allergenic extracts is obligated to recommend standards of effectiveness consistent with the available technology and readily obtainable through the use of clinical and laboratory methodology that has already been recognized by the general scientific community as practical and applicable to the products under review. FDA will publish a separate proposal concerning the reclassified allergenic extracts following its review of the advisory review committee's recommendations. (Also see item VIII.A.3. in FDA's response to this report.)

In the **Federal Register** of January 4, 1974 (39 FR 1082) and June 19, 1974 (39 FR 21176), FDA requested under § 601.25

data and information regarding allergenic extracts and related products.

Some concern has been expressed that the confidential information submitted to FDA under § 601.25 will become public information. Data and information submitted in response to the June 19, 1974 notice and falling within the provisions of 5 U.S.C. 552(b), 18 U.S.C. 1905, or 21 U.S.C. 331(j) have been handled by FDA as confidential. With the publication of this proposed implementation and the Panel's findings, however, such data and information will, under § 601.25(b)(2), be made publicly available after February 22, 1985, and may be viewed at the office of the Dockets Mangement Branch, except to the extent that the person submitting the data and information demonstrates that it still falls within the confidentiality provisions of one or more of the above statutes. Accordingly, comments concerning confidentiality should be submitted by February 22, 1985.

FDA appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of allergenic extracts and related products:

Panel Chairman, Paul M. Seebohm, M.D., Associate Dean, College of Medicine, University of Iowa, Iowa City, IA 52242.

Elliot F. Ellis, M.D., Professor and Chairman, Department of Pediatrics, State University of New York at Buffalo, Director, Clinical Research Center and Division of Allergy/Clinical Immunology, Children's Hospital, 219 Bryant St., Buffalo, NY 14222.

Ralph Hale, M.D., Clinical Assistant Professor of Internal Medicine, University of Kansas School of Medicine, 847 South Hillside, Wichita, KS 67211.

David A. Levy, M.D.,[1] Professor of Biochemistry, Johns Hopkins University, 615 North Wolfe St., Baltimore, MD 21205.

Frank Perlman, M.D., Clinical Professor of Medicine, University of Oregon Medical School, Portland, OR 97201.

Robert E. Reisman, M.D., Associate Clinical Professor of Medicine and Pediatrics, State University of New York-Buffalo, Associate Director, Allergy Research Laboratory, Buffalo General Hospital, 50 High St., Buffalo, NY 14230.

Thomas E. Van Metre, M.D., Associate Professor of Medicine, Johns Hopkins University, Physician in Charge, Allergy Clinic, Johns Hopkins Hospital, Rm. 8306, 615 North Wolfe St., Baltimore, MD 21205.

Dr. Frank Perlman's membership on the Panel ended on August 14, 1978, due to an illness which resulted in his death in 1979. Dr. Perlman participated substantially in the Panel process on all issues and working papers which resulted in the ultimate final report.

Two nonvoting liaison representatives served on the Panel. Mrs. Barbara Mae Hoover Layman, nominated by the Ragweed Erdication Program, Waynesboro, PA, served as the consumer representative. John Adams, Ph.D., of the Pharmaceutical Manufacturers Association, nominated by a number of producers with products under review by the Panel, served as the industry representative. Karl Bambach, Ph.D., or Charles B. Cleveland substituted for Dr. Adams during his absences. Morris Schaeffer, M.D., Ph.D., participated in the Panel meetings in his capacity as Director of the Office of Scientific Advisors and Consultants, Center for Drugs and Biologics, FDA. Clay Sisk, Center for Drugs and Biologics, FDA, served as Executive Secretary of the Panel.

In addition, the Panel employed a distinguished consultant, Max Samter, M.D., Director, Institute of Allergy and Clinical Immunology, Grant Hospital of Chicago, 550 W. Webster Ave., Chicago, IL 60614, whose continued advice and aid in developing the Panel report was invaluable.

The Panel was convened on May 24, 1974, in an organizational meeting. Working meetings were held July 12–13, 1974; August 16–17, 1974; October 11–12, 1974; December 6–7, 1974; January 17, 1975; March 7–8, 1975; April 25–26, 1975; June 13, 1975; August 8–9, 1975; October 3–4, 1975; November 7–8, 1975; January 16–17, 1976; February 27–28, 1976; April 23–24, 1976; July 23–24, 1976; October 29–30, 1976; December 10–11, 1976; February 11–12, 1977; April 15–16, 1977; May 20–21, 1977; July 22–23, 1977; September 30–October 1, 1977; November 11–12, 1977; January 13–14, 1978; April 7–8, 1978; May 25–26, 1978; July 13–14, 1978; September 28–29, 1978; January 12–13, 1979; April 27–28, 1979 and August 9–11, 1979.

Over 160 persons attended one or more meetings of the Panel and many participated in the open discussions. Every person who requested an opportunity was heard by the Panel. The names of these persons are on file with the Dockets Management Branch as listed in the Summary Minutes of each meeting.

The Panel submitted its final report to FDA on March 13, 1981. The report was made available to the public through a notice published in the **Federal Register** on April 21, 1981 (46 FR 22808).

The advisory Panel appointed to review data and information concerning safety, effectiveness, and labeling of allergenic extracts has completed its review as follows:

I. Products

The Panel on Review of Allergenic Extracts evaluated all data submitted for the following Allergenic Products classified as:

Allergenic Extracts (except those allergenic extracts made from bacteria which were reviewed by the Panel on Review of Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" (see 42 FR 58266 and 44 FR 1544))
Allergenic Extracts—Alum Precipitated
Poison Ivy Extracts
Poison Ivy Extracts—Alum Precipitated
Poison Ivy-Oak-Sumac Extracts Combined
Poison Ivy-Poison Oak Extracts Combined
Poison Oak Extracts
Poison Sumac Extracts
Histamine Azoprotein.

Data submitted for these products are cited by Biologics Efficacy Review (BER) Volume numbers. The volumes will be available in accordance with the provisions of 21 CFR 601.25(b)(2) at the Dockets Management Branch (address above).

II. General Statements

The charge to the Panel on Review of Allergenic Extracts under § 601.25 (21 CFR 601.25) was (1) to evaluate the safety and effectiveness of allergenic extracts and related allergenic products for which a license has been issued pursuant to section 351 of the Public Health Service Act; (2) to review the labeling of these biological products; and (3) to submit a report containing the Panel's conclusions and recommendations.

The Panel report, following the procedures in § 601.25(e), recommends that the pruducts be classified into one of three categories:

Category I includes those allergenic products determined by the Panel to be safe and effective and not misbranded. Inclusion in this category may be conditional on following recommendations relative to the active components, labeling, tests required before release of lots, product standards, or other conditions related to safety and effectiveness.

Category II includes those allergenic products determined by the Panel to be

[1] On July 1, 1975, David A. Levy, M.D., replaced Bernard B. Levine, M.D., Professor of Medicine, New York University, who resigned from the Panel.

unsafe or ineffective, or to be misbranded.

Category III includes those allergenic products determined by the Panel not to fall within either Category I or II on the basis of the Panel's conclusion that the available data are insufficient to classify such extracts and for which further testing is therefore required.

Category III is subclassified into: Category IIIA, a designation for those products determined by the Panel to have a favorable benefit/risk ratio and safe to remain on the market pending completion of testing to demonstrate effectiveness sufficient to be placed in Category I. For products placed in this category, the Panel has recommended the type of testing and has given guidance on the time period within which such testing might reasonably be concluded.

Products determined by the Panel to have an unfavorable benefit-risk ratio were placed in Category IIIB which is a classification for products needing further study, but because of questionable benefit and/or potential risk are recommended for removal from the market until the questions raised concerning each product are resolved by further study.

Category recommendations were made both on a generic basis and a product basis. A generic recommendation relied on the accumulated evidence and indicates the status of information about the substance. A recommendation for a company's licensed product was based upon the information which applies to that product only.

In the **Federal Register** of March 19, 1984 (49 FR 10168), FDA announced a reorganization that included the establishment of the Office of Biologics Research and Review as a component of the Center for Drugs and Biologics. Therefore, any reference in this report to the Office of Biologics, National Center for Drugs and Biologics, should be interpreted as a reference to the Office of Biologics Research and Review, Center for Drugs and Biologics.

A. Allergenic Extracts

Definition of Allergy and Rationale for Diagnosis and Treatment. Illness associated with exposure to foreign organic substances has been known to exist since the early part of the nineteenth century. The first recognized disorder was called hay fever because of its occurrence in the early summer or haying season. Since that time a number of conditions such as conjunctivitis, rhinitis, asthma, urticaria, vomiting, diarrhea, and anaphylactic shock have been shown to follow exposure to various substances either through contact, injection, inhalation or ingestion. This group of disorders, when allergic in nature, has a number of characteristics which are distinctly different from infectious and other types of diseases. Whereas infections are often widespread and severe upon the first encounter with human hosts, allergic symptoms do not appear until repeated contacts with the offending agent have occurred. Prior exposure is necessary to "condition" the host to react to subsequent challenges. Patients so conditioned are said to be sensitized or hypersensitive, a state which tends to persist and may remain latent for decades without repeated exposure. In 1906, von Pirquet (Ref. 1) coined the word "allergy" to define those conditions with an altered state of reactivity to some foreign substance.

Sensitized individuals exhibit symptoms on reexposure to the offending agent and often extremely small quantities of the substance will produce a severe reaction. Only a small proportion of individuals among many exposed become sensitized and exhibit symptoms on reexposure to the offending agent. About 15 percent of the populatioin becomes sensitized to such ubiquitous airborne agents as mold spores and pollens, but the remainder of the population seems to treat these agents as inert. Individuals with a tendency to develop allergic sensitivities are said to be "atopic." In the past 20 years, great progress has been made toward an understanding of the mechanisms involved in these disorders.

The basic steps in dealing with potentially allergic complaints are: first, to identify the clinical condition as being characteristic of one known to be associated with hypersensitivity mechanisms; second, to identify the specific sensitivities by appropriate test methods; and third, to treat the patient by recommending avoidance of the offending agent if this is practical, or if it is not, then to try to create tolerance in the host with appropriate drugs or by immunotherapy which consists of controlled administration of extracts of the offending agent.

Much of the early work in allergy dealt with the pollinoses. The association of certain symptoms year after year with the annual, well-defined pollinating season of various trees, grasses, and weeds was accepted as evidence of a cause-and-effect relationship. Reproduction of the same symptoms out of season by artificial challenge of the patients with specific pollens confirmed the relationship. A more convenient method of identifying the sensitive state was the direct skin test. When a small amount of pollen was rubbed into a superficial scratch in the skin an endematous (wheal) and an erythematous (flare) reaction developed in those patients known to have symptoms but not in those without symptoms. The substance (or substances) in the pollen grains which is responsible for this reaction was termed "allergen." Although the degree of skin reactivity to allergens did not always parrallel the clinical severity of the disease, the skin test did substantially separate the symptomatic from the asymptomatic population.

Early efforts to improve the skin test led to the solvent extraction of the allergenic components from the whole pollen grains and quantitative intradermal injection of the resulting solution, the allergenic extract.

By 1911, Noon and Freeman had demonstrated that sterile extracts of pollens could be used safely for skin testing and that repeated injections of the same extracts improved the clinical tolerance of sensitive subjects to natural exposure to the pollen (Refs. 2 and 3).

Ten years later, experiments revealed that one of the characteristic features of the allergic individual was the presence of a humoral factor (called reagin) thought to be an antibody, and more recently identified as immunoglobulin E (IgE). The presence of this factor was demonstrated by transfer of the allergic individual's skin reactivity into the skin of a nonallergic subject by an interdermal injection of the serum of the allergic patient and a later challange of the skin site with the appropriate allergenic extract, eliciting a positive reaction (Ref. 4).

The early experiences with hay fever demonstrated quite conclusively the effectiveness of pollens and their extracts as aids in the diagnosis of seasonal conjunctivitis, rhinitis and asthma, and empirical evidence mounted in support of the effectiveness of repeated injections of extracts in the development of clinical tolerance to the pollens.

The early experiences with the pollinoses were soon extended to the clinical study of nonseasonal rhinitis and asthma. A host of other environmental agents such as molds, animal hairs, and various dusts were extracted and used for testing and treatment. Additional disorders of the skin and gastrointestinal tract were studied for the association of symptoms with contact with a specific substance. Vivid examples of clincial sensitivity to some inhalants, for example, animal danders; to some foods, for example, seafoods and nuts; and to some drugs,

for example penicillin, were found to have a firm causal relationship.

In some situations, however, the direct association of symptoms with ingestion of a given food and/or skin reactivity to an extract of that food was difficult to establish. Likewise, many cases of rhinitis, asthma, and urticaria could not be proven to be caused by known allergens. Also, many patients without proven allergies have been treated with allergenic extracts and historically this may have contributed to the uncertainty concerning the effectiveness of allergenic extracts in the diagnosis and treatment of diseases known to be allergic in origin.

From the beginning of the practice of allergy it was recognized that testing and treatment were being performed with chemically crude preparations. While experience and scientific advances have resulted in gradual refinement of some of these earlier products, it is likely that for some years to come nearly all of the allergens in common use will be manufactured by making aqueous extracts from naturally occurring source materials. This procedure yields a product which is a crude and complex preparation. While the nonallergenic components are not desirable, at the same time they are not known commonly to interfere with the effectiveness of allergenic extracts. Furthermore, it is still too difficult and costly to remove these impurities to yield allergenic products without them. To date, only a very few allergens have been isolated in a relatively pure state. Recognition of this difference between allergens and most drugs is important and makes it unreasonable to require as stringent standards of purity for allergenic extracts as for single entity drug products. To require otherwise at this time would severely restrict the number of allergens available and would hinder the clinical management of allergic patients.

Over 1,500 substances which are extracted and licensed as allergenic extracts were reviewed by the Panel and generically classified in accordance with the following criteria. In general, most extracts were found through research or experience to be safe for use in humans and many are effective for skin test diagnosis. Those for which there is adequate evidence were placed in Category I.

Many extracts are used for diagnosis, but fewer are used for immunotherapy of allergic diseases. This is because many allergic disorders can be treated effectively by avoidance once the offending allergen has been identified. Unfortunately, of the extracts commonly used for treatment, only a small number have been subjected to acceptable scientific investigation aimed at establishing their effectiveness. Nevertheless, many allergenic products have been used to treat atopic patients who have been under the care of qualified physicians for many years, and there is empirical evidence for many that they are effective therapeutic agents.

Therefore, the Panel has recommended that the large proportion of these preparations be retained on the market and made available for continued use pending adequate standardization and further investigation to determine their effectiveness.

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(3) Freeman, J., "Further Observations on the Treatment of Hay Fever by Hypodermic Inoculations of Pollen Vaccine," *Lancet*, ii:814–817, 1911.

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B. Definitions

Definitions were established by the Panel for several words and phrases used in the review:

1. "Adjuvant" means a substance or combination of substances which can enhance or prolong immune responses. Aluminum hydroxide is an example of an immunological adjuvant.

2. "Antigen" means a natural or synthetic substance capable of eliciting an antibody or cell-mediated immune response or both; the term "antigen" is sometimes used synonymously with "allergen". However, while all allergens are antigens, not all antigens behave as allergens, particularly in some individual animals or man.

3. "Allergen" means an antigen, a natural or synthetic substance, or the active principle(s) therein or derived therefrom, which is antigenic (i.e., gives rise to an immunological reaction) and which has the capacity to produce a hypersensitivity reaction. Short ragweed pollen and ragweed antigen E are examples of allergens.

4. "Allergenic extract" means a preparation of an allergen obtained by extraction of the active constituents from animal or vegetable substances with a suitable menstruum. Short ragweed pollen extract is an allergenic extract.

5. "Allergenic product" means a biological product, including allergenic extracts and others, that is administered to man for the diagnosis, prevention or treatment of allergy and allergic disease. Short ragweed pollen extract and honeybee venom are allergenic products.

6. "Allergic disease" means a disease state or disorder mediated by an immune mechanism—in particular, those disease states or disorders mediated by antibodies of the IgE class. Allergic rhinitis/conjunctivitis due to ragweed pollen (also called ragweed hay fever) and anaphylaxis following a bee sting are examples of allergic diseases or disorders.

7. "Allergy" means a hypersensitivity state acquired through exposure to a particular allergen. Reexposure to the allergen reveals an altered capacity to react. Hypersensitivity reactions are pathological processes induced by immune responses. "Allergy" is sometimes used in place of "allergic disease."

8. "Cell-mediated immunity" is used to describe that group of immunological reactions mediated principally by immune cells (i.e., sensitized lymphocytes) and not their antibody products. Poison ivy dermatitis and a positive skin reaction to tuberculin are examples of cell-mediated immune reactions.

9. A "combination allergenic product" or a "fixed combination allergenic product" is an allergenic product which is prepared by extracting more than one source material to yield an allergenic extract or is an allergenic product which is prepared by mixing stock concentrates, each of which was derived from a single source material.

10. "Dating period" is used as in 21 CFR 600.3(1).

11. "Delayed type hypersensitivity" is a manifestation of cell-mediated immunity or a hypersensitivity state mediated by sensitized T (thymus derived) lymphocytes. After contact of a sensitized subject with antigen, e.g., by intracutaneous inoculation, lesions may not appear until about 12 to 24 hours, depending upon the degree of sensitivity of the host.

12. "Effectiveness" as applied to allergenic extracts means the ability to identify the presence of specific allergic sensitization, or to prevent, ameliorate, or modify the allergic state in a beneficial way. This definition encompasses the criteria of 21 CFR 601.25(d)(2).

13. "Established acceptance criteria" are the detailed written manufacturing specifications for a licensed allergenic product which shall be established in the product license file at the Bureau of

Biologics and within the manufacturing establishment.

14. "Expiration date" is used as in 21 CFR 600.3(m).

15. "Hyposensitization"—see "Immunotherapy".

16. "Immediate hypersensitivity" means a hypersensitivity state mediated by antibodies of the immunoglobulin E (IgE) class.

17. "Immunotherapy" is the practice of using allergenic products in the treatment or prevention of allergies and allergic diseases or disorders. Injections of short ragweed pollen extract administered repeatedly to a ragweed-sensitive individual is an example of immunotherapy.

18. "Potency" is used as in 21 CFR 600.3(s).

19. One "protein nitrogen unit" (PNU) is equal to 0.01 microgram of nitrogen in the solids precipitated from solution by phosphotungstic acid and determined by the microKjeldahl method. The PNU does not necessarily reflect the presence of allergenically active antigens in an allergenic product.

20. "Raw material" means a natural or synthetic substance used in the manufacture of biological products. Short ragweed pollen, chicken eggs, glycerin, and phenol are examples of raw materials used in the manufacture of allergenic products.

21. "Source material" means a raw material, as obtained naturally or synthetically or in a processed form, which contains allergen(s) and which is used in the manufacture of allergenic products. Short ragweed pollen, house dust, chicken egg whites, and leaves of poison ive are examples of source materials used in the manufacture of allergenic products.

22. "Stability" means the duration of allergenic activity of an allergen or allergenic product under various conditions of storage such as temperature, light, solvent, etc., including the effect of incorporated presevatives and adjuvants on this activity. Stability of an allergenic product implies the maintenance of potency over the dating period.

23. A "stock concentrate" in an allergnic extract or product derived from a single source material or from a combination product which is subsequently used in the manufacture of more than one lot of product, or from which dilutions or mixtures are prepared directly (after 21 CFR 680.3(b)(1)).

24. "Weight by volume" (w/v) is a traditional method for expressing the strength of an allergenic extract and refers to the original weight of the extracted source material per volume of extracting fluid usually expressed in grams per milliliters. As with a PNU, w/v does not necessarily reflect the presence of allergenically active antigens in an allergenic product.

C. The Use of Allergenic Extracts in Diagnosis

1. *Allergenic extracts for skin test diagnosis.* The ideal skin test should identify only those patients who, if exposed clinically to the allergen, have symptoms and should not detect responses in those subjects who do not have symptoms. It is recognized that the variables affecting skin testing include (1) the immunological system of the patient, (2) the test material, and (3) the test method.

Ideally, the immunological systems of the subjects in the allergic population should react positively in a uniform fashion to a constant stimulus and those of the control population negatively to the same stimulus. In actual fact, since no two patients are alike, a range of responsiveness can be expected in the allergic group.

To be effective, testing agents must be prepared by a reproducible method, have a known strength, and remain stable for a reasonable length of time. The diluent into which the testing material is dissolved must not elicit local or systemic reactions in the host.

Methods of testing must provide for the application of a measurable dose of extract to the skin, with minimal trauma and without provoking nonspecific physiological reactions in the skin.

The Panel recognizes that skin testing with allergenic extracts is actually the production of a local allergic response under limited and controlled conditions which, if not performed with due care, could result in a dangerous systemic reaction. In considering the safety of the products, the Panel assumed their administration to be performed by, or under the supervision of, skilled clinicians.

Aside from the biological activity associated with the use of extracts in testing, the Panel defined the characteristics of safety associated with the ideal skin test and compared the extracts with this definition. The ideal standard of safety would be a product that would produce no adverse effect, immediate or long-term, localized or systemic, major or minor.

Although immediate adverse effects are readily identified, long-term adverse effects could occur and not be readily recognized or assoicated with the product under consideration. However, after over 50 years of extensive use of allergenic extracts in testing and treating countless numbers of patients worldwide, no data have evolved showing long-term harmful effects to human tissue.

Considering the small amount of material used in the skin test and its application in a localized area of the skin, the Panel believes it is highly unlikely that any products reviewed have mutagenic or teratogenic properties. Similarly, after years of usage for testing and treatment, no evidence has evolved that carcinogenic effects are associated with aqueous allergenic extracts.

All allergenic extracts for skin test diagnosis submitted to the Panel were evaluated for both safety and effectiveness. However, many practical limitations must be recognized and are discussed in subsequent sections of this report.

2. *Diagnostic techniques*—a. *Skin tests for immediate hypersensitivity*—(1) *Introduction.* Blackley is credited with first using the skin test to identify the causative factor in seasonal hay fever (Ref. 1). It is now known that the skin test detects the presence of specific IgE antibodies fixed to mast cells in the skin of the allergic individual. The positive test is identified by the appearance of a local wheal and flare reaction within 5 to 10 minutes after the introductio of allergen into the skin. Positive reactions vary from several millimeters to several centimeters in diameter. Small reactions are raised and round; large reactions are often irregular in shape with prominent lateral projections called pseudopods. A positive test is characterized by localized edema surrounded by an area of vasodilatation and is usually accompanied by a sensation of local itching. The positive test usually peaks in 10 to 20 minutes and then gradually subsides over the next 30 minutes. Thus, it resembles the skin reaction to injected histamine in appearance (Ref. 4). Biopsies taken at the height of the reaction may reveal degranulated mast cells. Later biopsies may show neutrophils and eosinophils. The immediate skin response can be inhibited by antihistamines, but not by corticosteroids.

Late or delayed-in-time local reactions (which are not delayed hypersensitivity reactions) sometimes follow an immediate reaction, particularly when the latter is large. The late reaction begins in 3 to 4 hours, peaks in 6 to 12 hours, and clears in approximately 24 hours (Ref. 2). Histologically, the late reaction is characterized by infiltration of lymphocytes, eosinophils, and neutrophils. An increased number of basophils is also present. Histamine

alone does not cause a late reaction. Degranulation of mast cells or basophils appears to be necessary for the late reaction. Late reactions can be induced by immunologic (e.g., antigen-specific IgE or IgE-anti-IgE) and nonimmunologic (e.g., compound 48/80) mechanisms (Refs. 2 and 3). Late reactions can be inhibited by corticosteroids.

An excessive intracutaneous dose of allergen may provoke a systemic, anaphylactic allergic reation, especially in a highly sensitive individual. (See the section on safety for details.) Therefore, it is essential that those who perform diagnostic skin tests be adequately trained in the selection of appropriate doses of the allergenic extracts used in testing and in the administration of appropriate anti-anaphylactic treatment, which must always be on hand.

(2) *Allergenic extracts used in skin testing.* Allergenic extracts for skin testing are prepared either in an aqueous solution or an aqueous solution containing 50 percent glycerin. Fifty percent glycerin is not irritating on the surface of the skin or in a superficial scratch, prick, or puncture, but it is irritating when injected intracutaneously. Therefore, for intracutaneous testing, extracts should contain no more than 2 percent glycerin in order to avoid nonspecific irritation. In some very reactive patients, the concentration may have to be even lower, i.e., 0.6 percent or less (Ref. 5). Aqueous extracts can be used for either epidermal application or intracutaneous injection, but allergens (particularly in dilute solution) are less stable without glycerin, and therefore aqueous extracts require storage at 4 to 8° C to delay loss of potency. If glycerinated extracts are diluted with aqueous medium, they also become less stable and require similar handling. In practice, glycerinated extracts are preferred for surface application, and either dilute glycerinated or aqueous extracts are used for intracutaneous testing.

(3) *Methods of skin testing*—(a) *Cutaneous (percutaneous and eipcutaneous).* There are several cutaneous test methods which are designed to weaken the stratum corneum to facilitate penetration of an extract applied to the surface (Ref. 6).

(i) *The scratch test.* The scratch test consists of making a very shallow short cut into the skin with a sharp pointed instrument such as a hypodermic needle or a blade without drawing blood. A small drop of extract is then applied to the cut.

(ii) *The bore test.* In the bore test, as first described by von Pirquet (Ref. 7), the outer layer of the skin is disrupted when a blunt instrument with sharp corners is lightly pressed and twisted in a circular motion against the skin surface. The extract is then applied to the roughened area.

(iii) *The prick test.* In the prick test, as described by Lewis and Grant (Ref. 8), a drop of extract is applied to the skin and a small needle is inserted through the drop into the outer layer of the skin. The needle is then elevated so that the point breaks through the superficial layer of the stratum corneum.

(iv) *The puncture test.* The puncture test is a modification of the prick test in which a needle is pressed into the outer layer of the skin through a drop of extract, forming a small hole into which the extract is carried. With all of the methods, the excess extract is usually wiped away a few minutes after the test is made. When properly done, each of these cutaneous test methods is reported to be reliable and to have some advantage. Opinions concerning these methods vary, however, and it would appear that the skill, experience, and the preference of the physician or technician has much to do with the choice of one method over the other (Refs. 9 and 10).

(b) *Intradermal (intracutaneous).* In the intradermal testing technique, 0.01 to 0.05 milliliter (mL) of allergenic extract is injected into the superficial layers of the skin. As usually performed, the quantity of extract injected should be just enough to raise a small superficial bleb approximately 2 to 3 millimeters (mm) in size. Although the volume injected does influence the final wheal size (Ref. 11) the skin reaction does not depend as much on the volume as it does on the concentration of the allergen which is injected. An effort should be made to avoid penetrating into the subepidermal capillary bed of the skin.

(c) *Comparisons of skin test methods.* It is generally agreed that the cutaneous tests are less sensitive then the intradermal tests, a consequence of the much smaller volume of extract introduced by the former method. For this reason, more concentrated extracts are used with the cutaneous methods. Voorhorst and van Krieken (Ref. 14) studied the wheal and flare phenomena of the skin test and concluded that, based on measurements of wheal and flare reactions from multiple test sites, the intradermal test yielded more consistent results than the prick test. Other authors (Ref. 10) conclude that there is better agreement between the prick test and the existence of clinical allergy. Perhaps this is because the intradermal test is too sensitive an indicator of clinically significant disease. The cutaneous techniques are presumed to be safer because, in spite of the fact that stronger concentrations are used, the extract is on the surface where it can be wiped away if it appears that a large reaction is developing. The range of difference in dose effect between cutaneous and intradermal methods using allergenic extracts is estimated to be approximately 1 to 3 logs. This difference is reflected in the concentration of histamine used as a positive control. Thus, for cutaneous tests, 1 percent histamine phosphate is recommended whereas, for intracutaneous tests, 0.01 percent is used (Ref. 12).

To improve the accuracy of information obtained from skin tests, controls should be used routinely at the same time the tests are applied to the skin. Histamine is recommended as a positive control to learn if the skin is in a normally reactive state. Failure to react to histamine might signify improper application of the test or that the patient had recently taken medication which was inhibiting the reactivity of the skin. A negative control with the buffered saline diluent may also be used; however, if a number of tests are done, a negative reaction to an allergen which has been diluted identically to those giving positive reactions will also serve as a negative control.

(4) *Skin test sites.* The area of the skin on which tests are done is of some importance. In practice, three sites are generally used: the back of the thorax, the lateral surface of the upper arm, and the volar surface of the forearm. Cutaneous tests are usually applied on the back or on the forearm; intradermal tests are usually applied on the upper arm or on the forearm. There is a variation in reactivity of the skin depending on the site, but this is not regarded as a significant problem in clinical practice. However it is a problem when it is necessary to make accurate comparisons between the sizes of skin tests (Ref. 11), and in that case attention must be paid to this factor.

Tests with allergens are most reliable when performed on healthy skin. Skin tests on patients with atopic dermatitis frequently produce wheals with only small zones of flare (Ref. 4). Dermatographia, heavily scarred areas (as from acne), fresh sunburn, psoriasis, acute dermatitis, venenata, and a variety of other skin disorders may distort the skin test reaction.

(5) *Reading the tests.* As stated earlier, the immediate skin reaction reaches maximum intensity in approximately 10 to 20 minutes with the intradermal reaction usually reaching a maximum faster then the cutaneous. For the best results, the time interval

between applying the allergen and reading the response should be recorded. It is common practice to give the tests a number value, either 0, 1, 2, 3, or 4 plus, depending upon size of the wheal (induration), flare (erythema) and the presense or absence of pseudopods. A zero reaction is of course negative. A 1+ reaction is minimal and consists of a small wheal (1 to 3 mm in the cutaneous test and 2 to 5 mm in the intradermal test) and surrounding flare. A 2+ reaction is larger (3 to 6mm and 6 to 10 mm) than the 1+, but the wheal does not show pseudopods. The 3+ and 4+ reactions have larger wheals with pseudopods and larger flares. Alternative methods include direct measurement of the diameters of the reactions.

(6) *Interpretation.* With appropriate controls, a positive skin test suggests an antigen-antibody union on the surface of mast cells with subsequent release of mediators and their action on local tissues. However, a positive or negative skin reponse to a given allergen cannot be considered to be sufficient evidence of the presence or absence of clinical sensitivity to that allergen. The skin reaction is dependent upon a number of variables including the level of sensitivity, the dose of the allergen, and the physiologic state of the mast cells at the time the test is done. False-positive reactions can be obtained through nonimmunologic mechanisms, for example, the presence of histamine or nonantigenic histamine-releasing substances in extracts. Particularly difficult to interpret are positive tests induced by relatively concentrated allergenic extracts, indicative of low levels of sensitivity. In most cases, the clinical significance of such test results is unknown. Obviously there are problems in evaluating the importance of weakly positive skin tests. A positive skin test must be correlated with other findings, particulary the medical history and physical examination, to be considered clinically significant. For example, it has been reported that the prevalence of positive reactions to a few allergens may be as high as 50 percent in the general population (Ref. 5). On the other hand, when subjects with either allergic symtoms or a family history of allergy are excluded, rates as low as 5 percent have been observed (Ref. 15). At the same time a negative skin test does not necessarily mean that allergy has been ruled out (Refs. 16 and 17).

(7) *Comparison of skin tests with other diagnostic methods.* Because it is so important to identify the causative factors in allergic states, alternate diagnostic methods have been sought. These methods depend upon demonstrating the presence of preformed IgE antibody either attached to the tissues (see the subsequent discussions on Conjunctival Testing and Inhalation Bronchial Challenge) or in the circulating blood serum.

The first demonstration of circulating allergic (reaginic) antibody was done with the P-K (Prausnitz-Küstner) or passive transfer skin test (Ref. 21). This consists of drawing blood from the patient, separating the serum after the blood has clotted, and injecting a small quantity of the serum into the skin of a suitable nonallergic recipient. A number of skin sites can thus be sensitized and, after a delay of some (usually 24) hours, the sensitized sites are challenged directly with different allergens. Positive reactions will occur in the sensitized sites if the donor's serum contains IgE antibodies specific for the allergens injected. This method was once widely used in practice and was useful in research. It is used less frequently today because of the availability of the in vitro tests described below.

Several in vitro tests have been developed for circulating antibodies, but the only one of current importance is the radioallergosorbent test (RAST), a radioimmunoassay. Properly standardized RAST testing correlates well with other diagnostic methods, for example, skin testing and bronchial challenge, if the level of allergen-specific IgE antibody is relatively high; but when it is low, the correlation is not so good. These comparisions are discussed in greater detail in other parts of this document.

8. *Conclusion.* Although subject to interpretation because of the many variables discussed, and particularly because of lack of standardized allergenic extracts, skin test are nevertheless regarded as being a reasonably reliable, sensitive and, at present, the most practical method for confirming the diagnosis of a specific allergic state. Although a useful method for research, RAST cannot as yet be accepted as a substitute for the direct skin test.

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b. *Conjunctival testing*—(1) *Introduction.* Conjunctival, nasal, and bronchial challenge tests have been developed to demonstrate directly the effects of pollens and other inhaled allergens on the natual shock organs of allergic conditions. Much of both the theory and practice of allergy is based on the proof by these tests that allergic patients differ from nonallergic patients in their reaction to allergens and that allergens differ from nonallergens in their effects on allergic patients.

Conjunctival challenge tests have been used frequently for these purposes because the conjunctiva represents an easily observable surface and a natural site of the manifestations of hay fever.

(2) *Methods.*

(3) *Test materials*—(i) *Dry allergens.* A number of dried allergens have been employed for the conjuntival test, including pollen (Refs 1 through 6), finely micronized allergens prepared for scratch testing (Ref. 7), and freeze-dried pollen extracts (Refs. 8 and 9). Large, mechanically irritating particles and primary chemical irritants must be excluded by careful preparation and by appropriate tests in nonallergic subjects. Purity must be assured.

(ii) *Extracts.* Aqueous allergenic extracts have been commonly employed (Refs. 3 through 5, 10, and 11). Primary eye irritants such as glycerin must be excluded by appropriate preparation and tests in nonallergic subjects.

(4) *Application of test.* The patient is seated and instructed to look upward with his hed titled back. The lower eyelid is retracted. Either dry allergen or aqueous extract can be instilled in the eye. Dry allergens may be tapped into the conjunctival sac as from the flat side of a toothpick, or a drop of allergenic extract may be placed in the conjunctival sac. The patient keeps the eye shut for about 3 minutes. Immediately thereafter, if dry pollen or other dry allergen has been placed in the eye, a sterile cotton applicator is used to lift out the allergen which is usually found entrapped in a strand of mucous near the inner caruncle. It may be necessary at this time to wash out the conjunctival sac with a few drops of isotonic saline solutions.

(5) *Controls.* If dry allergen is tested in one eye, a negative control such as dry pine pollen may be taped into the other eye. If an aqueous extract is tested in one eye, diluent can be placed in the other to serve as a negative control.

(6) *Selection of concentration for testing*—(i) *Dry allergen test.* Under most circumstances, dry allergen conjunctival tests are not done unless the skin test is known to be negative or weakly positive. This avoids the producton of an excessive eye reaction in a patient who can be shown to have conjunctival IgE antibody by the gentler aqueous extract test (Ref. 5).

(ii) *Aqueous extract test.* In general, testing is begun with the same concentration already shown to produce a tolerable positive intradermal reaction. A more quantitative estimate of conjunctival sensitivity cay be obtained by titration techniques, using serial dilution of extracts.

(7) *Type of conjunctival reactions*—(i) *Traumatic inflammatory reaction.* This is due to nonspecific irritation of the eye by the procedure and may also be observed in the eye receiving the control substance (Refs. 1 and 5). This reaction usually involves the lower part of the ocular and palpebral conjunctivae and extends to the caruncle. It subsides within 3 minutes under most circumstances and therefore can be distinguished from the specific immediate allergic reaction described below. Difficulty in interpretation can ensue. however, particularly where the conjunctivae are irritable.

(ii) *Immediate allergic reaction.* This consists of redness of bulbar and palpebral conjunctivae persisting for more than 5 minutes after removing pollen or other dry allergen or 5 minutes after applying aqueous allergenic extract. The reaction may be severe and include chemosis of sclera, conjunctiva, caruncle, and even edema of the lids. These severe reactions are neither necessary nor desirable and can be avoided in most instances by: (1) Selection of appropriate challenge dose, (2) removal of pollen and particulate matter after three minutes of contract and putting one drop of epinephrine 1:5,000 in the eye as soon as a positive immediate allergic reaction has been clearly identified (Refs. 1, 5, and 12).

(ii) *Delayed allergic reaction.* A delayed reaction may appear after 12 to 24 hours, where an immediate allergic reaction did not occur or occurred and cleared (Refs. 1 and 5). For this reason, it is recommended that only one allergen be tested during each 24-hour period, a severe limitation to the use of the test for general diagnostic purposes.

(iv) *Variable reactions to conjunctival test.* The sensitivity of the conjunctiva varies in the same patient from time-to-time (Refs. 8 and 13) so that a stronger concentration of an aqueous extract is required to produce a positive reaction at one time than at another. An increase in sensitivity has been noted when the conjunctivae are irritated or infected, when the test subject is under emotional distress, and when the conjunctivae ar reacting to allergens naturally present in the ambient air at the time of the test (Ref. 8). This variability has frustrated attempts to use the method as a gauge of relief of sensitivity by immunotherapy or medication.

(8) *Indications.* The conjunctival test has been performed for the following indications:

(i) *Challenge (provocation) testing.* Since allergic conjunctivitis is a common and well recognized feature of the hay fever syndrome, conjunctival testing has been used as a method for inducing the disease under controlled circumstances. This method has been useful for testing the reactivity of one natural shock organ, the eye, to potential inhaled allergens and has been employed for studying hay fever due to allergy to allergens such as the pollens of grass (Refs. 11 and 14), ragweed (Ref. 11), plantain (Ref. 15), poplar (Ref. 16), ailanthus (Ref. 17), oak (Refs. 16 and 18), hickory (Ref. 16), birch (Ref. 16), beech (Ref. 16), elm (Ref. 16), ash (Ref. 16), sycamore (Ref. 16), maple (Ref. 16), linden (Ref. 19), mesquite (Ref. 20), Japanese cedar (Ref. 21), cypress (Ref. 22), and Japanese hop (Ref. 23). It has also been used to study hay fever due to allergy to *Alternaria* (Ref. 24).

The method will demonstrate eye reaction to allergens in allergic patients. Fineman (Ref. 11) has shown unequivocally that patients clinically sensitive to grass and ragweed pollens have positive conjunctival and skin (cutaneous and intracutaneous) reactions to extracts of these pollens. The skin test has the advantage of supplying the same information as the eye test, and has other distinct advantages. Multiple skin tests to many allergens can be done at a stitting, but only one allergen can be tested in 24 hours by the conjunctival method. Skin reactions are rarely influenced by the irritants and emotional stimuli which modify the conjunctival test.

The eye challenge test is useful when hay fever symptoms occur in a patient exposed to multiple potential allergens simultaneously, of which one, some, or all may be important, and the physician wishes to know whether eye symptoms of hay fever can be induced by the

allergen (Ref. 16). The method was much used by the early pioneers to evaluate an abundant pollen which was not yet known to be allergenic. Pine pollen was evaluated in this manner. It is produced and is airborne in enormous quantities. Yet this pollen almost never produces an immediate allergic conjunctival reaction and therefore can be used as a control test of the reaction of the eye to a nonallergen (Refs. 1 and 5).

Also, the method has been used to detect so called local sensitivity or immediate allergic reaction in the conjunctivae existing in the absence of skin reactivity. This is a rare phenomenon when skin reactivity is measured by intradermal testing with equivalently strong extracts, but is fairly common when scratch or prick skin tests have been done (Ref. 5) for the reasons demonstrated in Fineman's studies (Ref. 11), which have been discussed above. Such reactions must be interpreted with great caution in view of the large number of factors which may induce false positive skin and eye tests when strong extracts are employed. As a general rule, diagnosis of an IgE mediated allergic reaction is more certain when both skin and eye tests are reproducibly and repeatedly positive to low concentrations of allergenic extract.

(ii) *Titration of sensitivity.* The response of the conjunctiva to a given allergen has been quantitated by titration techniques, using serial dilutions of extracts. This method was introduced by Noon (Ref. 14) who used dilutions of grass pollen extract to show the decrease in conjunctival senstivity following, and presumably in consequence to, a series of injections of grass pollen extract. Feinberg, Stier and Grater (Ref. 8) have studies this method also. To this date, no one has devised a satisfactory method to control the variations in conjunctival sensitivity associated with irritation, infection, allergic reactions to naturally occurring allergens in the ambient air, and emotional factors so that the effects of one variable such as immunotherapy can be studied in a satisfactory manner.

(9) *Conclusion.* Conjunctival tests are cumbersome, and only one allergen can be tested reliably in a 24-hour period. Under most circumstances, they provide the same information obtained from skin tests which can be done more rapidly and permit testing many allergens in a 24-hour period. The end point of the conjunctival test may be difficult to read, painful, and variable. It depends on many factors other than the specific allergen tested, which can influence the reactivity of the conjunctiva such as irritants, infection, naturally occurring allergens in the ambient air, and emotional factors. However, where carefully done with appropriate concentrations of allergen in highly allergic subjects, they may supply essential information with reference to the allergic reactivity of one natural shock organ and the allergenicity of potential allergens in the ambient air.

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c. *Inhalation bronchial challenge*—(1) *Introduction.* The discrepancies in the relationship between clinical histories in some patients and skin test reactions have created an interest in the development of other methods for allergy diagnosis. Direct application of the suspected allergen to the "shock organ" is one which has been received with varying degrees of interest and enthusiasm in the United States for the past 4 decades (Refs. 1 through 4). In Europe and especially Scandinavia, a number of investigators have expressed the opinion that provocation testing by inhalation bronchial challenge is indispensable for allergy diagnostic evaluation in patients with asthma (Refs. 5 through 8). Furthermore, initiation of immunotherapy, by their standards, is indicated only in those patients who have been studied by this method and have been shown to have positive tests (Refs. 6 and 7).

Of the three tissues used for mucous membrane testing with suspected allergens—conjunctival, nasal, and bronchial—the first two are rarely used today either clinically or for research purposes. On the other hand, bronchial mucous membrane testing has been receiving considerable attention in the past few years in this country (Refs. 9 through 13). The principal uses of bronchial provocation testing are as an aid in arriving at an accurate etiologic diagnosis, an aid in assessing the results of immunotherapy and as a laboratory model of asthma.

At the outset, it should be recognized that asthma induced in the bronchial challenge laboratory is not identical to the spontaneously occurring disease. For example, naturally occurring asthma of the allergic variety follows inhalation of

particulate allergens, whereas the allergens tested in laboratory-induced asthma are extracts of the raw materials and are in solution. In one study, for example, bronchoconstriction developed in only 4 of 8 patients who inhaled 200 to 1,500 ragweed pollen grains. When the 4 negative reactors were then challenged with an aqueous extract of 800 pollen grains, bronchoconstriction was induced (Ref. 14). Nonallergenic irritative phenomena, atmospheric changes, viral respiratory infections, and psychologic factors have an influence on the natural disease which cannot easily be reproduced in the usual laboratory test situation. Although estimates have been made in an attempt to quantify natural allergen exposure, the magnitude of this exposure is most often unknown, as is the amount necessary to produce symptoms. The doses of allergen administered to the patient in bronchial provocation testing have been determined quite arbitrarily and may not represent an amount likely to be encountered in the natural setting. However, there are many pathophysiologic features of laboratory-induced asthma that are similar to the spontaneously occurring disease. These features, revealed by spirometric testing, include decreased capacities and flow rates, increased airway resistance shown by body plethysmography, decreased lung compliance, increased pulmonary artery pressure, abnormalities in distribution of ventilation, and blood gas abnormalities.

The principal limitations of bronchial provocation testing have to do with technical, interpretive, and safety considerations. The method is technically demanding and time consuming. Interpretation is difficult because airway hyperactivity is an intrinsic part of asthma. Positive reactions observed may represent nonimmunologic stimulation of the airways during the test procedure rather than being immunologically specific and occasionally a severe and persistent attack of asthma can be provoked as a result of the provocation procedure.

(2) *Methods.* While many variations in methodology are recorded in the bronchial provocation literature (Refs. 8, 9, 10, and 13), the principal is the same. Preparations of allergenic extracts in aqueous diluents are aerosolized using a compressor and a nebulizing device. A specially designed dosimeter has been developed by Rosenthal (Ref. 12) to assure consistent delivery of the inhaled solution. Patients are studied when asymptomatic and when their baseline forced expiratory volume in 1 second (FEV_1) is 80 percent or greater than their highest previously recorded value. Adrenergic agents, theophylline, cromolyn, antihistamines, and cholinergic blocking agents are withheld for varying periods of time before the test procedure. Patients on stable doses of corticosteroids may be tested. Baseline pulmonary function measurements are obtained several times before and after inhalation of diluent solution alone to ensure that the patient's airways are not reacting to either the expiratory effort itself or in response to the inhaled control solution. If the subject's airway reactivity is stable during the control period, he/she is challenged with increasing concentrations of allergen solution. Spirometry (or another measure of pulmonary function response) is done at the end of the inhalation of each concentration and 5 to 10 minutes later. If there are no changes in pulmonary function and no subjective symptoms of asthma appear, the next higher concentration of extract is inhaled. Upon evidence of a decrease in pulmonary function or the appearance of subjective symptoms, measurements are made approximately every 5 minutes until a definite trend is seen. A reduction in expiratory flow of 20 to 25 percent, for example, which is maintained for at least 15 minutes, is considered to be a positive response. Most often, the reduction in pulmonary function will not be accompanied by significant subjective symptoms, but if they occur, the patient is treated with bronchodilator solution by inhalation. Generally, not more than one test per patient is conducted during a 24-hour period. If a test is positive, subsequent challenges are not done for at least 48 hours.

A committee of the Asthma and Allergic Disease Centers has published a standardized bronchial inhalation challenge procedure designed to resolve some of the differences of interpretation due to differences in technique (Ref. 10). While some more sophisticated measures of pulmonary function have been used in recording the bronchial response, these techniques are more time consuming and are not deemed to be worth the additional trouble because they provide little additional information in the clinical setting beyond that derived from tests measuring various aspects of expiratory flow such as spirometry and peak flow (Ref. 9).

(3) *Results.* There have been a number of studies that compare the results of bronchial challenge testing with in vivo and in vitro tests which measure specific IgE antibody (Refs. 9 and 15 through 21). There are a few reports of positive bronchial challenge responses in the presence of negative skin tests, suggesting that a variation in local reactivity may exist (Refs. 3 and 22). But the majority of investigations, particularly those done in a more quantitative fashion, indicate that a negative skin test is only very rarely associated with a positive bronchial response (Refs. 9 and 23 and 24). On the other hand, only positive skin tests obtained by the puncture method or by intracutaneous tests with very dilute extracts can be corroborated by positive bronchial challenges (Refs. 11 and 18). There are excellent correlations between radioalergosorbent test (RAST) results, in vitro leukocyte histamine release results, and results of bronchial challenge testing (Ref. 11). From the foregoing, it may be concluded that bronchial challenge testing for diagnostic purposes is only rarely indicated in clincial practice. Selection of allergens for inclusion in an immunotherapy regimen can be rationally accomplished on the basis of the results of radioimmunoassay, puncture, or intradermal tests. Rarely, if ever, will an allergen be shown to be of clinical significance by bronchial challenge in the face of negative skin and RAST tests.

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d. *Skin testing for cell-mediated immunity.* Cell-mediated immunity refers to that group of immune reactions mediated by sensitized lymphocytes and not their antibody products. Once considered to be primarily the delayed hypersensitivity reaction associated with certain infections as demonstrated classically by the tuberculin reaction, cell-mediated immunity now is known to be a much more complex immunologic phenomenon that is expressed not only in delayed hypersensitivity but also in a number of biologic events of potential clinical significance. Additionally, because sensitized lymphocytes play some role in the development of humoral (antibody-mediated) immunity, cell-mediated immunity is not as functionally independent of immediate-type hypersensitivity as it was once thought to be.

Clinically, delayed hypersensitivity is demonstrated by intradermal injection of antigen (e.g., purified protein derivative, or PPD, or tuberculin) which induces in the sensitized individual a raised, red, indurated local reaction beginning about 6 to 8 hours later and reaching a maximum after 24 to 48 hours. A positive reaction indicates prior infection with the source of the antigen, i.e., the microbes. For example, a positive skin test to PPD is evidence that the individual has had an infection (often subclinical) with tubercle bacilli or has been immunized with attenuated tubercle bacilli vaccine (BCG). As the incidence of tuberculosis in the United States has decreased and a large segment of the population has not been exposed to the organism, the effectiveness of this skin test in case finding has been greatly enhanced. Previous clinical experience with the use of tuberculin in the treatment of active tuberculosis showed that it was ineffective.

A number of other bacterial, fungal, and viral products which can elicit delayed hypersensitivity have been used in the diagnosis of infection with the corresponding organisms. None has proven to be as useful as tuberculin, and most, because of the almost universal exposure to certain organisms (e.g., the streptococcus), have been relatively little value in diagnosis.

However, some of these materials have taken on new significance since the discovery of a variety of abnormalities of the immune system (e.g., immunodeficiencies) and with the widespread use of potent drugs, such as in the treatment of malignancies, which supress the immune system. For example, children lacking a normal thymus gland (DiGeorge syndrome) have no cell-mediated immunity. Cell-mediated immunity is often impaired in patients with sarcoidosis and lymphosarcoma. Several bacterial, viral, and fungal antigens are widely used now in skin testing to determine the functional integrity of the immune system and as an aid in the differential diagnosis of these disorders.

Vast experience with some of these skin test antigens has shown that healthy people will reach to at least one. The commercially available antigens currently in use include tuberculin PPD, candidin, trichophytin, epidermophytin, coccidioidin, histoplasmin, streptokinase/streptodornase and mumps, some of which are licensed as allergenic extracts. Skin test surveys have shown that over 90 percent of normal American adults exhibit at least one positive reaction to a panel of these antigens (Ref. 1).

To be accurate in establishing the competence of the cell-mediated immune system:

(1) The antigen should be a stable biological of standardized potency (e.g., PPD).

(2) The antigen should induce an area of induration which varies in size with the dose of antigen.

(3) Reactivity should be reproducible on repeated testing.

(4) The antigen should not induce an immediate hypersensitivity reaction that might interfere with the delayed hypersensitivity reaction.

(5) The delayed hypersensitivity skin test should not significantly alter humoral or cell-mediated immunity, i.e., it should not convert a negative reactor to a positive one, in a later test with the same antigen. If this occurred, widespread use of the test might interfere with the validity of diagnostic and epidemiologic studies with that antigen.

Patients who do not react to the commonly used skin test antigens can be tested for competence of the cell-mediated immune system by other means, for example by attempting to induce active sensitization by applying a known sensitizer on the skin or by the use of certain *in vitro* tests.

Skin testing for delayed hypersensitivity is a simple and inexpensive diagnostic procedure, and it is useful in the evaluation of immunocompetence. The Panel believes that useful skin test antigens of good quality should be available for this purpose. None of the currently licensed allergenic extracts are standardized or labeled for use in evaluation of cell-mediated immunity, although some are frequently employed in this manner. The Panel recommends that standardized

products labeled for this purpose be developed and licensed.

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D. The Use of Allergenic Extracts in Therapy

1. *Allergenic extracts for immunotherapy.* The treatment of allergic conditions with injections of allergenic extracts has been a widespread medical practice for over 60 years.

The earliest effective use of allergenic extracts in the treatment of allergic disease was reported in 1911 by Noon and Freeman. Repeated injections of extracts in doses small enough to avoid systemic reactions were given before the pollen season. The observed clinical improvement was thought to be parallel to the protection afforded guinea pigs against anaphylaxis after multiple small sublethal doses of antigen. The reduction of symptoms in patients following the injections led to naming the treatment desensitization. Further studies of patients showed that although they had fewer symptoms there was persistence of the skin reactivity which was attributed to unneutralized antibody which suggested that "hyposensitization" was a more appropriate term than "desensitization." However, since the mechanism of protection remained uncertain, a simple description of the treatment method, namely, injection treatment, was also used for many years. Although the precise mechanism of improvement following injections of allergens remains unknown, it has been established that a number of immunological changes do take place. "Immunotherapy" best describes the character of the treatment and is currently the most generally accepted term.

The evidence of effectiveness of immunotherapy ranges from controlled clinical investigations of the treatment of seasonal hay fever to partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. There are very few double-blind placebo-controlled studies reported, but the literature abounds with anecdotal reports of large numbers of patients that benefited by treatment who were used as their own control.

Immunological studies of treated patients show that specific IgG antibody production rises, histamine release by specifically sensitized leukocytes diminishes, and, over long periods of time, specific IgE antibody levels decrease. Such measurements reveal that a high level of biological activity is generated by the administration of allergenic extracts.

The beneficial effect of immunotherapy has been studied intensively for many years, and a number of different immunological changes have been observed, but none of these changes consistently correlate with the relief of symptoms. The IgG antibody which is produced is called *blocking antibody* because it can combine with antigen and block its interaction with cell-bound IgE antibody. Initially, IgE antibody levels are often transiently elevated and later, with prolonged treatment, gradually reduced. Leukocyte histamine release by allergen may be decreased as a consequence of treatment.

The concentration of blocking antibody has been found to be correlated with the quantity of antigens administered. The degree of relief from symptoms has also been shown to be allergen-dose related. Treated patients as a group have higher IgG antibody titers and fewer symptoms, but within the group the highest IgG titers are not necessarily found in the serum of patients with the least symptoms.

The methods of manufacture and storage needed to produce extracts of predictable potency for use in quantitative treatment schedules are known for some allergens which have been tested in clinical trials.

The major weakness in the evidence for effectiveness of treatment is in the lack of quantitation of the degree of exposure patients have to inhalant allergens. This defect is inherent in all clinical trials, and is one for which there are few practical methods of control. Substances such as pollens and some mold spores can be counted, but dusts and danders lack sufficient characterization to identify in a quantitative manner. Even in the case of pollens, the exposure of any given patient will vary greatly with his or her behavioral pattern and the level of control of the air in the home, automobile, office, etc.

For these and other practical reasons, the double-blind, placebo controlled experiment is a logistically difficult test for the effectiveness of many of the allergenic extracts. As a result, the Panel has had to rely heavily on "documented clinical studies by qualified experts, and reports of significant human experience during marketing" (21 CFR 601.25(d)(2)) in evaluating the evidence of therapeutic effectiveness of allergenic extracts.

In making its determination of the degree of evidence of effectiveness of the allergenic extracts for therapy, the Panel followed the principles outlined below:

a. *Substantial evidence*—(1) *Conclusive.* (i) Extract has been shown to be effective for skin test diagnosis;

(ii) Clinical data show a reduction of symptoms due to allergen exposure in patients receiving immunotherapy with a standardized potent extract as compared to a placebo-treated group in a well-designed and conducted controlled study; and

(iii) Specific immunologic changes occur as a result of immunotherapy, such as:

(*a*) A rise in serum allergen specific immunoglobulin G (IgG);

(*b*) The rise of serum allergen specific IgE, which occurs normally as a result of allergen exposure, is inhibited;

(*c*) Allergen specific IgE as measured by in vitro and in vivo tests is decreased; and

(*d*) Histamine release from specifically sensitized leukocytes is decreased on allergen challenge.

(2) *Acceptable.* (i) Extract has been shown to be effective for skin test diagnosis;

(ii) Controlled studies have not been done, but long experience by qualified allergists suggests effectiveness in therapy, and the clinical picture associated with its use is documented according to modern standards; and

(iii) Demonstration of specific immunologic changes, as a result of immunotherapy, such as:

(*a*) A rise in serum allergen specific IgG;

(*b*) The rise of serum allergen specific IgE, which occurs normally as a result of allergen exposure, is inhibited;

(*c*) Allergen specific IgE as measured by in vivo and in vitro tests is decreased; and

(*d*) Histamine release from specifically sensitized leukocytes is decreased on allergen challenge.

b. *Circumstantial evidence.* (1) Extract has been shown to be effective for skin test diagnosis;

(2) Long experience by qualified allergists suggests effectiveness in therapy, but controlled studies have not been done; and

(3) Immunologic studies have not been done.

c. *Insufficient evidence.* (1) Extract has not been shown to be effective for skin test diagnosis;

(2) Extract may have been associated with clinical improvement in selected patients, but the clinical picture associated with its use is not documented according to modern standards; and/or

(3) Extract does not produce immunological changes, or if such changes do occur they are not appropriate for, nor would they be expected to benefit, the condition being treated.

d. *Category determinations.* The extracts meeting the above criteria of "substantial, conclusive evidence" have been recommended for Category I.

Some extracts for which there is substantial but not conclusive evidence because of a lack of controlled studies of the reduction of clinical symptoms have been designated as acceptable for Category I if:

(1) The reported long experience of qualified allergists has shown the extract to have had widespread acceptance and use;

(2) The clinical picture associated with its use is documented according to modern standards;

(3) Favorable immunologic changes have been shown to occur with treatment;

(4) Systematic observation of possible adverse effects has been made; and

(5) The natural history of the disease for which it is used is generally well understood.

The Panel regards the intervening years of use along with evidence about the above parameters as providing an acceptable indication of safety and effectiveness, despite lack of double-blind controlled symptom reduction trials. The Panel thus recommends such extracts for Category I on a generic basis. Continued marketing of such extracts should be conditional upon each manufacturer's compliance with recommendations relative to active components, labeling, tests required before release of lots, product standards, or other conditions related to safety and effectiveness as they are developed. When a manufacturer's product has been demonstrated to be comparable to a product of proven safety and effectiveness, it should be placed in Category I.

The extracts that have been shown to be effective for skin test diagnosis and have had widespread acceptance and use by qualified allergists, but lack controlled clinical studies and demonstration of specific immunologic changes associated with their administration were considered to have only circumstantial evidence of effectiveness. The Panel recommends that these extracts be placed in Category IIIA permitting continued use pending further study of effectiveness.

Extracts for which there is insufficient evidence of either clinical effectiveness or immunological activity have been placed in either Category II or IIIB depending upon the data demonstrating ineffectiveness or lack of safety or upon the nature of the substance and the ratio of benefit-to-risk expected with its continued use.

2. *Immunotherapeutic techniques*—a. *Techniques of extract administration.* The sensitivity of the patient has greatly influenced the techniques of administering allergenic extracts. Because each injection dose is itself an allergic challenge, it is necessary to start with small doses. Generally, the more sensitive the patient, the smaller is the dose of allergen tolerated, particularly at the initiation of treatment. As in most other immunological procedures, effective antibody production is dependent on the size of the antigen stimulus. To achieve a substantial stimulus with allergens it is necessary to give multiple injections, usually 15 to 20, of the very small doses of allergen. Most patients develop a progressive tolerance to the extract so the dose can be increased with each injection. Such increments vary between 25 to 100 percent of the previous dose depending upon the patient's degree of sensitivity and the response to the previous dose.

Historically, treatment has been administered according to a variety of different schedules and at a variety of different times in relation to seasonal symptoms.

"Coseasonal" therapy is the administration of allergen injections when the patient is having symptoms from a seasonal allergen. The doses of allergen are very small and increased very little above the initial dose. The injection interval is usually between 2 to 5 days. This form of treatment has not been proven to be effective.

"Preseasonal" therapy is a method that starts with injections 4 to 6 months before the season of allergen exposure. Injections are given every 4 to 7 days in increasing amounts until a maximum tolerated dose of extract is established which is maintained or slightly reduced through the season. Any protection against the allergen and tolerance for the dose of extract that is obtained by this method can be sustained throughout the year by giving the maximum tolerated dose at 2-to-4-week intervals until the next season. Such treatment is called "perennial" therapy. Some physicians have the impression that perennial therapy is equally or more effective than annual preseasonal therapy. Perennial therapy may also be employed where the exposure to the allergen is sporadic or perennial.

Accelerated schedules with several injections on the same day, sometimes called the "rush" method, also have been reported and have been recommended for use with newly introduced *Hymenoptera* venom solutions. Labeling recommendations for the currently licensed products reviewed by the Panel do not include this method.

The duration of therapy is generally gauged by the patient's response. The duration of treatment of the average patient is 3 to 5 years. Treatment is often discontinued after patients become symptom-free for 1 to 3 years.

After the end of treatment, the duration of benefit varies greatly among patients. For many it is long lasting, but others relapse and treatment may be reinstituted.

The perennial administration of aqueous whole extracts remains the most common mode of immunotherapy currently practiced. Other modes of treatment are discussed subsequently in this document.

b. *Modifications of immunotherapy.* The effectiveness of immunotherapy appears to be closely related to the amount of allergen administered, but the patient's sensitivity may greatly limit the amount of allergen that can be injected. If the absorption of the allergen is slowed, the dose can be increased with reduced risk of provoking large local or systemic reactions. Delayed absorption can be accomplished with alum-precipitated extracts. It has been attempted with emulsions of allergenic extracts employing alginate or mineral oil, but these are not licensed biologicals. If the allergens are altered to reduce their allergenicity but retain their immunogenicity, increased doses can be achieved. Reduced allergenicity has been accomplished in research studies by treating pollen extract with formaldehyde (formalin) or glutaraldehyde, which permits injecting larger doses than is possible with aqueous extract.

E. Safety of Allergenic Extracts

1. *General statement.* Allergenic extracts have been and are widely used throughout this country. It is estimated that hundreds of thousands of diagnostic skin tests and injection treatments are given yearly to many patients with few reports of adverse reactions. If adverse reactions do occur they are primarily allergic in nature and are manifested by generalized skin erythema, urticaria, pruritis, angioedema, rhinitis, asthma, tachycardia and hypotension, but rarely by severe life threatening anaphylaxis

and even more rarely by death. The reactions are mainly due to the interaction of allergen (antigen) with IgE-specific antibodies, but other causes have not been excluded, e.g., endotoxin. These reactions usually occur within minutes following allergen administration, but may not begin until several hours later and may last a day or two. Other types of reactions resulting from prolonged immunotherapy, such as immune complex disease and malignancy, have been suggested as theoretical possibilities but not documented. Continued observation of patients receiving immunotherapy may be necessary to exclude such unanticipated adverse reactions.

a. *Allergic reactions*—(1) *Reactions associated with testing.* While available data may be incomplete, thorough literature review, information obtained from NIH-sponsored Allergy Clinical Centers and from extensive personal communications indicate that severe systemic allergic reactions resulting from diagnostic tests are of low incidence.

Education of physicians and technicians regarding proper testing techniques, proper use of allergens of high potency, identification of patients at greater risk, and standardization of extracts by the manufacturers are factors which would minimize the frequency of reactions following diagnostic skin testing.

Reports of 14 fatalities due to diagnostic testing have been found, all of which occurred over 20 years ago. The intradermally administered substances involved in these fatalities include an animal-derived glue, egg white (2 cases), buckwheat, horse serum (2 cases), antitetanus serum, a mixture of silk, wool and kapok, guinea pig hemoglobin, cottonseed, and "multiple" tests (3 cases) (Refs. 1 through 13). A fatality due to mustard extract was reported verbally by C.E. Arbesman, M.D., Buffalo General Hospital, in the 1950's.

The incidence of systemic reactions following diagnostic testing is exemplified in two reports. Van Arsdel and Sherman (Ref. 14) reported the incidence of systemic reactions among 8,706 patients receiving an unspecified but larger number of intradermal tests. Twenty-four patients reacted to ragweed, four to ragweed and grass, four to trees, two to cottonseed, two to several inhalants, one to a combination of mugwort and marshelder, one to a combination of grass, plantain, and birch, one to cosmos and dahlia, one to tomato and pork, and one to an unknown food. Thus, there were 42 patients with systemic reactions, an incidence of 0.49 percent. Cooke (Ref. 2) reported 11 systemic reactions due to diagnostic testing substances in 10 of 578 patients. Three reactions were to glue, two reactions to ragweed pollen, and one each to linseed, timothy pollen, orris, dog saliva, flaxseed, and mustard. A poll of eight asthma and allergic disease centers by the Panel found that systemic reactions to diagnostic extracts were of very low incidence. One center reported 1 reaction among 3,000 patients tested over a 5-year period. The Panel is unaware of any allergy clinic or physician that regularly monitors the incidence of adverse reactions due to diagnostic skin testing.

(2) *Reactions associated with treatment.* Systemic reactions (e.g., tachycardia, hypotension, death) occur with varying frequency following injection treatments. The Panel estimates that such reactions occur with an incidence of less than 1 percent. Only 7 deaths following injection therapy have been found, but in all probability others may have occurred. Ragweed pollen extract was involved in 4 of these fatalities (Refs. 13, 15 and 16). C.E. Arbesman, M.D., Buffalo General Hospital Clinic, has verbally reported a fatality involving grass extracts which occurred about 1950. A. Scheffer, M.D., verbally reported one death involving dust extract. Ralph Hale, M.D., a Panel member, had knowledge of a patient death in 1968 in which multiple antigens were involved but not conclusively established to be the cause of death.

The reported incidence of systemic reactions following immunotherapy is summarized in the following tables:

TABLE I.—INCIDENCE OF SYSTEMIC REACTIONS FOLLOWING IMMUNOTHERAPY

	Year	Number of reactions	Injections		Patients		Remarks
			Number	Reactions (percent)	Number	Reactions (percent)	
Arbesman and Reisman office	1974	2	555	0.37	300	0.67	
VanArsdel and Sherman (Ref. 14)	1935–1955	1,774	1,250,000	.14	[1] 8,706	7.6	15 percent of total pollen sensitive reacted.
Gay (Ref. 17):							
Vander'Veer et al	1926	96	14,280	.67			All pollen injections.
Waldbott and Ascher	1932–1935	141	51,036	.27			
Johns Hopkins Hospital Clinic	1930–1936	75	29,574	.25	[2] 522	8.0	
Cooke and Vander Veer (Ref. 18)	1916			3.75	339	29	
Figley (Ref. 19)	1930	10	2,000	.5	65	15	Perennial Rx.
Furstenberg and Gay, (Ref. 20)	1930–1936	87	43,771	.2	[3] 907	4.9	Pollen patients as above.
Cooke, (Ref. 2)	1920	94	5,416	1.7	[4] 578	10	
Pollen injections		82	4,215	1.9	[5] 310	15	
Levine (Ref. 32)	1979	94	[6] 64,000	1.5	[6 7] 425	15	

[1] 663 reacted, 635 pollen sensitive.
[2] 42 reacted.
[3] 45 reacted.
[4] 57 reacted.
[5] 48 reacted.
[6] Number not given but calculated from data in the report.
[7] 64 reacted.

TABLE II.—INCIDENCE OF SYSTEMIC REACTIONS FOLLOWING IMMUNOTHERAPY WITH RAGWEED AND ANTIGEN E (REF. 21)

Investigator	Antigen E		Ragweed	
	Cases	Reactions	Cases	Reactions
Arbesman (1965–1966)	34	5	25	9
Bernstein	11	1	3	0
Mosko	16	2	0	0
Norman (1966)	27	2	16	6
Seebohm (1965)	6	0	6	2
Seebohm (1966)	6	0	7	1
Totals	100	10	57	18

The Panel polled eight asthma and allergic disease conters concerning systemic reactions to immunotherapy. Three centers had no figures, though one stated "very low incidence." The other 5 centers reported these rates: 4 per 3,000 injections; 1 per 2,400 injections; 150 per 66,123 injections; 1 or 2 mild reactions per month out of 25,000 injections administered per year, and 0.1 percent or less. None of these centers reported any deaths due to immunotherapy. To some extent the systemic reaction rate in immunotherapy in related to the type and dose of administered extract. Despite all appropriate precautions, a very low systemic reaction rate is probably inevitable if presently recommended guidelines for immunotherapy are followed. Attempts to administer allergenic extracts to patients at the highest tolerated doses are likely to lead to increased incidence of systemic reactions (Ref. 32).

b. *Possible long-term adverse effects of immunotherapy.* There is one case report of cutaneous pseudolymphoma occurring at the site of administration of house dust and bacterial vaccine injections (Ref. 22). These allergens were given for about 1 year before the lesions appeared.

Two papers presented at the 1976 meeting of the American Academy of Allergy raised questions regarding the possible adverse effects of long-term immunotherapy. Raphael et al. (Ref. 23) measured the latex agglutinating activity in the sera of 56 atopic individuals receiving hyposensithization therapy for at least 12 onths and in a control gourp of 30 atopic ssubjects who had never received immunotherapy. Fourteen of 56 study sera and 2 of 30 control sera were positive by at least 1 of 2 commercial slide screening tests for rheumatoid factor. Five sera, all in the study group, gave titers of 1:40 to 1:50,120 using the Singer-Plotz latex agglutination method with overnight incubation of 4°C. The authors suggesed the possibility that production of antiglobulin activity may be a consequence of hyposensitization therapy.

Kohler reported four patients with "asthma" who were treated with hyposensitization for presumptive inhalant allergies and subsequently developed mononeuritis multiplex and arteritis. No direct evidence linked hoposensitization treatment with development of arteritis. Asthma and eosinophilia may have been the initial manifestation of the arteritis (Ref. 24).

In two further studies, Stein et al. (Refs. 25 and 26) studied 50 patients with allergic rhinitis who were receiving immunotherapy and 2 control gourps. One control group consisted of 25 patients with allegric rhinitis not receiving immunotherapy and the second group consisted of 25 healthy volunteers. Laboratory procedures included serum C3 and C4 levels, rheumatoid factor, urine protein, and detailed analysis of cryoglobulins. Results may be summarized as follows: (a) no proteinuria was found either before or 2 hours after immunotherapy; (b) several patients in each group had a positive rheumatoid factor but there was no difference in the incidence between groups; (c) positive cryoglobulins were found in all 3 groups. The incidence of positives in groups 1, 2 and 3 were 22 percent, 28 percent and 24 percent, respectively. Chi square analysis demonstrated no statistically significant difference in incidence. This study concluded there is no evidence of circulating immune complexes or immune complex disease as a result of immunotherapy.

Levinson et al. (Ref. 27) studied 41 atopic patients receiving hyposensitization and 15 atopic controls. Laboratory studies included urinalysis, CBC, SMA12, sédimentation rate, serum protein electrophoresis, rheumatoid factor, antinuclear factor, immunoglobulins, cryogolbulins, T and B lympphocytes, C3, C4, and circulating immune complexes. The authors could find no evidence of coliical sequalae related to long-term therapy. A few abnormal immunolgical responses were found including 2 patients in the treatment group with positive antinuclear antibody (ANA) and 2 with positive direct and indirect Coombs test reactions. In the control group a single positive ANA was found. This study also suggested that long-term immunotherapy was safe although the authors recognized the necessity for monitoring patients who develop abnormal immunologic findings.

c. *Use during pregnancy*—(1) *Allergic reactions.* Uterine contractions have been described as part of the systemic reaction occurring following allergen administration (Refs. 28, 29, and 31). There is a report of one case of abortion occurring following a grass pollen injection (Ref. 28). In the discussion of this report, Vander Veer states he has seen 1 or 2 other similar reactions.

(2) *Possible effect on the fetus of immunotherapy administered during pregnancy.* The major source of information concerning the relationship of allergenic extracts administered during pregnancy and fetal malformations is the Boston Collaborative Drug Surveillance Program (Ref. 30). The authors concluded:

> In our study, cohort of 50,282 mother-child pairs, there were a total of 125 pregnancies exposed to at least one allergenic extract at any time during gestation. Details of the individual preparations and their usage rates are attached in Table I. Unfortunately the numbers are insufficient to enable one to make any definitive statement.
>
> The exposed pregnancies resulting in malformations together with the gestational age at exposure are listed in Table II. The overall rates of relvant malformations are presented in Table III. Examination of these data suggests that insofar as any excess of malformations occurred, it was accounted for by 2 cases of pectus excavatum (where 0.2 cases would be expected), and three cases of isolated inguinal hernia (where 1.7 cases would be expected).
>
> This observation is difficult to interpret since in the cohort these two malformations show substantial inter-institutional variability in their rates of diagnosis. We believe that a large subjective component exists in the diagnostic criteria for these particular outcomes, which is reflected in the above mentioned variability. In fact we have elected to consider these malformations separately in all our analyses.
>
> With respect to other defects, we observe that two malformed infants (#1 and #5 in Table II) were born of pregnancies in which an exposure to allergenic extracts occurred during the first trimester. There were 74 such pregnancies. This malformation rate (2.7%) is not excessive since the overall rate in the Collaborative Perinatal Project data is about 4.5%. It should be noted that this latter rate excludes certain defects including pectus excavatum and inguinal hernia (see Table III).
>
> We do not regard the data presented here as being very helpful in providing solid information concerning possible effects of allergenic extracts. Firstly, the numbers involved are too small, and, secondly, the malformations occurred in excess are difficult to diagnose, because of poor diagnostic criteria.
>
> However, despite our reservations and qualifications regarding certain aspects of the data, we do not believe that the safety of these preparations is in any sense established.

TABLE I.—EXPOSURES TO ALLERGENIC EXTRACTS

Preparation	Number of exposures	
	Any	First trimester
Allergy shots [1]	106	64
House dust extract	15	10
Poison ivy extract	5	2
Poison oak extract	3	3
Grass pollen extract	2	0
Black widow spider extract	1	0

[1] The preparation—Allergy Shots, Allergy Tablets, Endo-dust, Ragweed Endo-dust, Ragweed Extract, Ragweed Pollen Antigen, and Vaccine #48—were all originally assigned the same code.

TABLE. II.—MALFORMED CHILDREN BORN TO EXPOSED MOTHERS

Preparation(s) used	Gestational age at exposure (lunar months)	Malformation(s) in offspring
1. Allergy shots	1 to 10	Bilobed lung, hypoplastic intestine, multiple cardiac defects.
House dust extract.	8 to 10	
2. Allergy shots	3 to 9	Pectus excavatum.
House dust extract.	3 to 9	
3. Allergy shots	1 to 10	Pectus excavatum.
House dust extract.	1 to 10	
4. Black widow spider extract.	5	Absence of limb or part.
5. Allergy shots	1 to 10	Hydrocele, inguinal hernia.
6. Poison ivy extract.	7	Inguinal hernia.
7. Allergy shots	Unknown	Malignant tumor.
8. Allergy shots	2 to 4	Inguinal hernia.
House dust extract.	2 to 4	
9. Allergy shots	5 to 10	Aortic stenosis, hypospadias.
10. House dust extract.	7	Congenital duodenal bands.
11. Allergy shots	1 to 4	Inguinal hernia.

TABLE III.—RATE OF CERTAIN MALFORMATIONS—THE STUDY COHORT (50,282 CHILDREN)

	Number	Rate per thousand
Any malformation	3,248	64.6
Any malformation with acceptable inter-institutional variability	[1]2,277	45.3
Cardiac malformations	404	8.0
Inguinal hernia	683	13.6
Pectus excavatum	92	1.8

[1] Excludes children whose only malformations were inguinal hernia, pectus excavatum, clubfoot, isolated cleft gum and urethral obstruction.

NB: Five of the malformed children whose mothers were exposed to allergenic extracts are in this category.

These data suggest that at the present time there is no documentation of possible teratogenic effects of allergenic extracts administered during pregnancy. The data, however, are too insufficient to reach a firm conclusion that allergenic extracts are safe for administration during pregnancy.

A retrospective study of the risk of immunotherapy during pregnancy was recently reported at the American Congress of Allergy and Immunology (Refs. 29 and 31). The abstract of this work is as follows:

In order to determine if the use of immunotherapy (IT) during pregnancy adversely affected the mother or the fetus, the records of 71 atopic females who had received IT to the common inhalant antigens during 88 pregnancies were reviewed. The data obtained from obstetrical records and/or a questionnaire completed by the mother. There was no evidence for uterine hemorrhage, stillbirth, or neonatal death. The rate of toxemia was 2.3%, of abortion, 5.7% and of prematurity (37 weeks), 4.6%. Each of these was less than half that for the general population. The rate of congenital malformations (4.5%) was slightly higher than the general population (2.3%), but equal to that for a similar group of atopics who were not receiving IT during pregnancy. Seven mild generalized reactions were noted during these 761 months of IT.

These data indicate that there is no increased risk to the fetus or mother who is treated cautiously with IT during a normal pregnancy.

d. *Summary*—(1) *Diagnostic skin testing.* Allergenic extracts used in accordance with generally accepted principles of diagnostic skin testing are associated with minimal acceptable risks. Systemic allergic reactions following rarely occur.

(2) *Immunotherapy.* Allergenic extracts used in accordance with generally accepted principles of immunotherapy are safe. Systemic allergic reactions following injections of allergenic extracts occur in low incidence and usually are self-limited or are controlled readily with medication. There is no reliable evidence at present of any undesirable adverse effects resulting from prolonged immunotherapy. There is no evidence at the present time of adverse effects of immunotherapy given to pregnant women on the fetus.

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2. *Mycotoxins*—a. *Introduction.* There is considerable evidence indicating that mycotoxins produced by molds may poison man and animals. Some have been known since antiquity. These include ergot poisoning, which is manifested by gangrene, abortion, and death. This has been caused by eating rye and other grains parasitized by *Claviceps purpurea*, a mold which makes ergot in large quantities (Ref. 1). In addition, mushroom poisoning has been well known to result from eating either *Amanita muscaria*, a mushroom which produces the powerful parasympathomimetic muscarine, or *Amanita phalloides*, a mushroom which elaborates the deadly hepatotoxins, phalloidine and amanitine (Ref. 2).

In recent years, mycotoxin poisoning has been identified with increasing frequency (Refs. 3 and 4). In field outbreaks, the trouble is often seasonal, because particular climate sequences favor toxin production by the mold. Some poisonings have been associated with a specific food such as peanut meal, rice, or corn, and the examination of the suspect food has revealed signs of fungus activity. More than 200 mycotoxins have been shown to be capable of causing disease in animals and/or man, and it seems likely that more will be found (Refs. 4 and 11).

Some of the more important mycotoxins which have not yet been discussed include:

(1) *Aflatoxin* (Refs. 12 through 21). This toxin has been widely studied, and it is one of the most potent poisons known. It is produced most commonly by *Aspergillus flavus*, but may be produced by other molds including *Aspergillus parasiticus* and *Pencillium puberlum*. These molds produce aflatoxin when growing under natural circumstances on peanut, cottonseed meal, Brazil nuts, coca beans, corn, rice, sorghum, and soya. Aflatoxin has been shown to cause hepatitis and biliary cirrhosis in man, and there is considerable epidemiologic evidence indicating that it causes carcinoma of the liver in man. It has been shown to produce hepatitis and biliary cirrhosis in monkey, turkey, duck, chicken, pig, calf, trout, rat, hamster, rabbit, guinea pig, and dog, and carcinoma of the liver in monkey, trout, rat, and mouse. It has been shown to induce sarcoma at injection sites in the rat. It has been shown to produce benign hepatoma in the mouse.

(2) *Steroid toxins.* Steroid toxins (Ref. 7) are produced by *Fusarium, Cladosporium, Alternaria, Penicillium*, and *Mucor* when growing under natural circumstances on wheat, rye, oats, and buckwheat. They have been shown to cause alimentary toxic aleukia when ingested by man, mice, and cats which is manifested by nausea, vomiting, diarrhea, and profound and potentially fatal bone marrow depression with pancytopenia.

(3) *Stachybotrys toxin* (Ref. 8). This is produced by *Stachybotrys alternans* when growing naturally on hay, straw, and plant debris. This toxin affects man and produces ulceration of mouth, salivation, and bone marrow depression, with pancytopenia, anemia, agranulocytosis, thrombocytopenia, and death. Similar effects have been noted in horses, sheep, calves, swine, mice, guinea pigs, dogs, and chicks.

(4) *Islandotoxin and luteoskyrin* (Ref. 9). These toxins are produced by *Penicillium islandicum* when growing on rice. They have been shown to produce hepatitis, cirrhosis, hepatoma, and pancreatitis in mouse and rat.

(5) *Sporidesmin* (Ref. 10) is produced by *Pithomyces chartarum* when growing on rye hay. It has been shown to produce photosensitivity, facial edema, cholangitis and periportal hepatitis in sheep, cattle, guinea pigs, and rabbits.

Mycotoxins can be produced by the specific molds which are used in the preparation of mold spore extracts which are employed for skin test diagnosis and immunotherapy of patients with hay fever and/or asthma after inhaling specific mold spores. Mycotoxins can be produced by specific molds which commonly contaminate house dust, pollens, epidermals and foods which are used for making allergenic extracts. Since mycotoxins can produce very serious untoward effects in man, they must be carefully considered in determining the safety of allergenic extracts.

A review of the manufacturers revealed considerable variation in the methods used for dealing adequately with mycotoxin contamination. In many cases, the exclusion of mycotoxins from products is a result of well conceived and executed quality control measures. In other cases, the conclusion that products are free of mycotoxins is assumed to occur without actual testing.

It is important that manufacturers be aware of the potential mycotoxin problem and that only actual starting material or product assays are sufficient to prove the absence of mycotoxin. Commonly used methods short of assays have great limitations in mycotoxin control.

The standard short-term FDA animal safety test will not reveal low-level aflatoxin contamination, certainly not at extract levels below about 100 parts per billion. A special day-old duckling-assay test may be used, but it is not standard. Acetone extraction or washing (may) remove most of the aflatoxins, but the degree of removal cannot be determined without analytical work. Exposure of culture to light in the growth and extraction periods will not in the least affect aflatoxin levels. Ultraviolet light will cause some degree of aflatoxin decomposition, but only when the toxin is exposed while absorbed on a silica gel surface. While some natural substrates are the best media for aflatoxin production, the toxins can be produced in synthetic or semi-synthetic media with little difficulty. Aflatoxins may contaminate foods which by the naked eye appear mold-free and of high quality. While many manufacturers do not use *A. flavus*, the mold cultures they do use must be protected from inadvertent *A. flavus* contamination.

b. *Methods for control of mycotoxins in allergenic extracts.* (1) Certain methods apply to the control of all mycotoxins, but vary depending on the type of extract.

(i) *Mold extracts.* Specific mold spore extracts must be prepared by methods which exclude mycotoxins. Mycotoxin production usually demands that a toxigenic strain be grown under specific conditions. For example, aflatoxin is produced only by certain strains of *Aspergillus flavus*. It is produced in large quantities when these toxigenic strains are grown on a favorable media such as peanut meal, but in small quantities or not at all when the same strains are grown on synthetic media (Ref. 5). The elimination of mycotoxins from mold extracts starts with the use of

well-characterized strains of antigenically specific molds which are nontoxigenic when grown under precisely defined conditions with reference to media, volume, containers, temperature, time, etc., harvested, washed and extracted in a precisely defined manner.

Autogenous mold spore extracts which have been made from strains of molds and under conditions which have not been characterized with reference to mycotoxin production might be expected to present unacceptable hazards from potential mycotoxins.

(ii) *House dust extracts.* Contamination of house dust by toxigenic molds is inevitable. Mycotoxin production can be controlled by preventing mold proliferation by promptly dehydrating freshly collected house dust and storing it in airtight containers before extracting. Use of house dust extracts which have been made from damp house dust which has been allowed to overgrow with molds between collection and extraction might present a potential hazard from mycotoxins.

(iii) *Pollen and epidermal extracts.* When collected, pollens and epidermals should be more free of molds than house dust, but they will inevitably be contaminated. Both antigenic purity and mycotoxin production can be controlled by rapid dehydration and storage in a dry state.

(iv) *Food extracts.* Foods like mushrooms, which are molds, should be selected from varities which are edible and free of known toxins. Foods should be free of spoilage and in a fresh state normally considered mycotoxin-safe (Ref. 6) when collected. They should be dried as soon as collected and stored in a dehydrated state in airtight jars at room temperature. Alternatively, they may be frozen and stored at −5°C or less.

(2) Other methods apply particularly to the control of specific mycotoxins.

(i) *Aflatoxin.* (*a*) The potential for aflatoxin contamination of allergenic extracts is very low. Most important among the reasons for this conclusion is the fact that aflatoxins are very poorly soluble in aqueous media.

(*b*) The above conclusion must be treated cauticusly, for there is no way to assure that aflatoxins are completely excluded from extracts unless it is ascertained by actual assay that the material from which the extract was made (mold, food, etc.) does not contain aflatoxins, or if these do contain aflatoxins, it must be determined by actual assay of the final products that the mode of preparation has eliminated aflatoxins.

(*c*) It is possible to determine the presence of aflatoxins at very low levels either in starting materials or final products, and manufacturers of extracts should incorporate some degree of use of such assay procedures into their production operations.

(*d*) Because of the extremely potent biochemical effects of the aflatoxins, even in the low ppb range, it is critically important that manufacturers of any product which has the potential, however slight, for becoming aflatoxin contaminated and to which humans might be exposed take extreme care in avoiding conditions which might lead to contamination and inchecking the quality of their starting materials and products.

(ii) *Mcyotoxins other than aflatoxin.* Much less is known about other mycotoxims and their potential for harm for humans and about appropriate assays. Control depends on vigorous application of the general methods for preventing fungus proliferation and, mycotoxin production which have been described above.

Final extracts should be studies at least for the toxins listed in Table 1.

TABLE 1

Toxin	Producing fungus
Zearalenone	*Fusarium roseum* (=*Gibberella zeae*).
Trichothecenes (T-2 toxin).	Many genera, esp. *Fusarium.*
Patulin	Many genera.
Ochratoxin	*Aspergillus ochraceus.*
	Penicillium viridicatum.
Sterigmatocystin	*Aspergillus versicolor.*
Penicillic Acid	Many genera.

c. *Recommendations.* FDA should determine whether mycotoxins are detectable in a large selective sampling of extracts that might potentially be contaminated and identify those for which assay of each final lot is to be prescribed.

Because mycotoxins represent a potential hazard in allergenic extracts used for skin test diagnosis and immunotherapy, the following procedures are recommended for the manufacturers.

(1) *Mold extracts*—(i) *Aflatoxin control in Aspergillus flavus and other mold extracts.* (*a*) A mold strain and defined media and culture conditions which have been shown not to produce aflatoxin should be employed.

(*b*) The mold should be washed or extracted with acetone before the aqueous extraction.

(*c*) The final extract should be checked for aflatoxin by analytical methods such as those suggested by the Association of Official Analytical Chemists with a sensitivity of 0.5 to 5.0 ppb, depending on the commodity and approved by FDA.

(ii) *Mycotoxin control other than for aflatoxin.* (*a*) Modl strains, defined media, and culture conditions which have been shown not to produce known mycotoxins should be employed.

(*b*) The mold should be washed or extracted with acetone before aqueous extraction.

(*c*) Analyses of the final extracts should be performed on those extracts which may be prescribed in the future by the FDA.

(2) *House dust, pollen, epidermal and food extracts*—(i) *Aflatoxin control.* (*a*) Control mold proliferation in stored material before extraction by the following procedures:

House dust. Store the source material in dry state at room temperature, or without moisture control at −5° C or less.

Pollen. Use pollen which passes standard microscopic standards for purity and identity prescribed by FDA. Store the pollen in a dry state at room temperatue, or without moisture control at −5° C or less.

Epidermals. The sample should be clean and pure and stored in a dehydrated state at room temperature, or without moisture control at −5° C or less.

Foods. Source materials should be bought in clean and fresh condition and stored in a dehydrated state at room temperature, or without moisture control at −5° C or less.

(*b*) Assay the final extract for aflatoxin if prescribed in the future by FDA.

(ii) *Mycotoxin control other than for aflatoxin.* (*a*) Control mold proliferation in stored material before extraction as recommended above for aflatoxin control.

(*b*) Assay the final extracts if prescribed in the future by the FDA.

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3. *Endotoxins.* Endotoxins may be present in allergenic extracts because of bacterial proliferation in the source material or during processing of the extracts (Refs. 1 and 2). Endotoxins are integral parts of gram-negative bacteria, being derived from the cell wall and not released until after the death of the cell (Ref. 3). The bacterial cell wall consists of a comparatively small amount of peptidoglycan covalently linked to lipoprotein which contains repetitive sequences of non-polar amino acids, but no histidine, glycine, proline, phenylalanine, or tryptophan. Endotoxin is the outermost part of the cell wall, a lipopolysaccharide which is covalently bound to the lipoprotein. While the linkage of the various cell wall components is only partially known, the integrity of the lipopolysaccharide appears to be essential for its toxic effects (Ref. 13).

Endotoxin molecules can be divided into three regions. Region I contains an O-specific polysaccharide; region II is a "core" polysaccharide; and region III is a "Lipid A" or the crucial glycolipid which accounts for most of the known toxic effects of endotoxin.

The O-specific polysaccharide (region I) is identical with the somatic O-antigen within the cell; it is water-soluble, antigenic, but is not toxic. Region III, or Lipid A, is not water-soluble, not antigenic, but is toxic (Ref. 22).

The toxic effects depend upon the species from which the endotoxin is derived. Endotoxin from *Salmonella abortus equi*, for instance, produces comparatively weak reactions in Limulus amebocyte lysate tests, but its activity as a pyrogen in the rabbit is three times as high as the activity of endotoxin derived from *Escherichia coli* (Refs. 10 and 20). Endotoxins are heat stable.

Although endotoxins cause a variety of reactions, their biological functions are unknown. The spectrum of the known effects of endotoxins has been discussed in the review of the FDA panel on bacterial vaccines and antigens (42 FR 58275 and 58276; Nov. 8, 1977). Substantial amounts of endotoxins released suddenly can produce gastrointestinal hemorrhages, severe diarrhea, shock, and death. Even so, endotoxins are far less toxic than exotoxins. In smaller doses, endotoxins cause fever, leukopenia followed by leukocytosis, hyperglycemia, circulatory disorders possibly associated with an increased release of catecholamines and various expressions of the Shwartzman phenomenon (Refs. 4. 9, 12, and 13). Repeated injections of sublethal doses produce "tolerance," not only to a specific endotoxin, but to all endotoxins, as well as to traumatic shock and radiation injury. It is generally held that this is due to activation of the reticuloendothelial system and rapid clearance of injected endotoxin. Such tolerance, however, is short-lived. The endotoxin complex as a whole is antigenic, but the resulting antibodies do not inactivate the part of the complex which causes tissue damage in experimental animals.

In principle, small amounts of Lipid A—released from gram-negative bacteria which contaminate raw material—might affect the immunological response. It is difficult, however, to assess benefits which could be attributed to the contaminant (e.g., a lessened incidence of infection in patients treated with house dust extract (Ref. 15)). It is unlikely that the endotoxin contamination involves a significant clinical risk, judged by the safety record of allergenic extracts which have been marketed and used over many decades (Refs. 7 and 20). It is interesting that Brighton and Topping (Ref. 5), of the United Kingdom National Institute for Biological Standards and Control, in a very careful analysis of the diversity of house dust extracts, do not even mention endotoxins. Whether endotoxin levels and allergenic activity of the extracts are related is still open to question (Refs. 2 and 17). It has been suggested that endotoxins per se could induce false-positive skin reactions, but reliable data are not available.

Contamination of allergenic extracts with endotoxins is not limited to house dust extracts, but might well be found in extracts of farm dusts, wood dusts, vegetable fibers, animal danders, and perhaps to a lesser degree, in a fairly wide variety of allergenic extracts.

A comprehensive inquiry into the dimension of the problem-answered by individual investigators and centers of research on the makeup of allergens—yielded (1) general agreement that the problem exists; and (2) an astonishing diversity of opinions about how it should be handled.

Areas of agreement. Most authors agree with Berrens (Ref. 3) that 1 gram of house dust may contain up to 200,000,000 gram-negative organisms; that the endotoxin levels in house dust extracts, while variable, are significant (Ref. 24); and that fever and leukocyte changes caused by *E. coli* endotoxin and house dust extract are similar (Ref. 15). Attempts to dissociate the effects of antigens and endotoxins on human lymphocytes were not really helpful. One particular antigen under study (Antigen E) is a mitogen; endotoxin alone or added to antigen did not induce any demonstrable changes. Whether this is equally true for different antigens, or different concentrations of endotoxins, is not known. The problem, however, is under active investigation (Refs. 6 and 7).

Agreement, then, exists (1) that endotoxins are common contaminants of allergenic extracts, particularly extracts of house dust; (2) that this contamination is undesirable, but

probably innocuous; and (3) that data which have been obtained from carefully designed studies of the effects of endotoxins on experimental animals cannot be used for the prediction of the effect of small and variable amounts of the contaminant on the immunological response of atopic patients who are treated with allergenic extracts.

Areas of disagreement. Consultants who disagree with a "laissez faire" attitude toward the presence of endotoxins in allergenic extracts can be roughly divided into two groups: (1) those who feel that—for the sake of purity—allergenic extracts should not be permitted to contain contaminants, and that the question whether the contaminant is of potential benefit or risk is not a relevant question; and (2) those who concede that a small amount of contaminant is permissible (e.g., up to 0.1 milligram (mg) endotoxin as a maximal amount for the total injected dose of the extract (Ref. 10)), or that the presence of contaminants should be noted on the label.

The controversy has been brought into sharp focus by two recent developments: (1) the availability of the Limulus amebocyte lysate test; and (2) the development of procedures which can remove endotoxins without affecting the potency of the purified allergenic extract.

The Limulus test is widely used. It will demonstrate the presence of endotoxin, but it is only "semi-specific"; in other words, a negative test means that the extract does not contain endotoxin, but a positive test might be the result of various nonendotoxin contaminants, i.e., gel-producing enzymes or enzyme activators (Refs. 7, 8, and 23). Nevertheless, it has been proposed—by Aas (Ref. 1) that for the time being, a note on the label should indicate whether the extract is Limulus-positive or Limulus-negative in order to permit prospective evaluation.

The second advance which might lead to the elimination of contaminants from allergenic extracts within the near future is the effectiveness of newly designed filtration systems which permit passage of comparatively small-molecular antigens, but retain comparatively large-molecular endotoxins (Refs. 11 and 17).

In summary, significant endotoxin levels are known to be present in house dust extracts and probably in other extracts. It is possible to prepare house dust extracts with low endotoxin levels but with adequate allergenic activity. The Panel believes that it is too early to insist on mandatory filtration which might be proven to be necessary at a future date. The Panel considered recommending the adoption of a mandatory Limulus amebocyte lysate test—with results to be placed on the label—but agreed to defer a recommendation pending further studies on the influence of endotoxins on the clinical performance of allergenic extracts. Meanwhile, manufacturing steps for allergenic extracts should be designed to limit bacterial contamination and thus reduce the opportunities for the development and release of endotoxins.

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F. *Labeling of Allergenic Extracts*

The principal objective of labeling (including package inserts) of an allergenic extract is to provide the physician with the information he/she must have to use the material safely and effectively as either a diagnostic or therapeutic agent. The physician needs reliable information concerning therapeutic indications, mechanism of action, routes of administration, and incidence and nature of adverse reactions. In general, only information based upon substantial evidence should be included in the labeling. Exceptions may be made in instances where rigorous proof of a particular point is not available, but is widely accepted by critical investigators and clinicians with at least some support from the scientific literature.

The package insert is not intended to include the sum total of knowledge about a product, but simply to be an authoritative document which contains only those indications and usages based upon substantial evidence of safety and effectiveness. To include references to indications or usage for which the latter

evidence is not available is neither lawful nor in the interest of good patient care.

Labeling shall contain the essential scientific information for safe and effective use of the product. The indications and recommendations for usage shall be based upon sound scientific evidence of efficacy and safety derived from human experience whenever possible. The information shall be accurate, nonpromotional, and neither false nor misleading in any sense. Allergenic extracts, at the time of consideration by this Panel, have not been labeled in accordance with recently published FDA proposals (Ref. 1) or regulations (Ref. 2). Either little or no information at all has been provided characterizing the active components of the extracts by either in vivo or in vitro methods. Recommendations concerning indications and usage have been lacking. Contraindications for usage, warnings, and precautions have been inadequately dealt with.

Adverse reactions are virtually ignored in most labeling. The consequences of overdosage are described in some inserts, but the specific heandling of the acute problem is inadequately detailed. Essentially, most allergenic extract package inserts provide dosage and administration information. Even here, many contingencies are not covered.

1. *Package insert recommendations.* Labeling of allergenic extracts may be designed on a generic basis for each category of extracts made from biologically and etiologically similar allergens, e.g., pollens, molds, etc., or, where more specific information is available, for extracts of a specific substance. In either instance, the package insert and other labeling must follow the regulations published by FDA. The most recent publication available to the Panel at the time it reviewed labeling was an FDA proposed regulation (Ref. 1) which was used as a guide for this evaluation. The principles of that proposal as applied to specific allergenic extracts are paraphrased by the Panel as follows:

1. Description.

Name: to include category of extract (e.g., pollen, mold, etc.).

Name of specific extract: (e.g., short ragweed pollen).

Other information describing the nature of the extracted source material (such as type of processing or the animal or plant part).

Dosage form, route of administration to which labeling applies.

Sterility statement, therapeutic class, physical properties (e.g., pH, etc.).

2. Clinical pharmacology.

This section should include:

a. Summary of data concerning the immunologic activities of the extract derived from both *in vivo* and *in vitro* studies in humans.

b. Information concerning present knowledge of mechanism of action with appropriate disclaimers where theory is not supported by factual data.

c. Pharmacokinetic information.

i. Bioavailability, i.e., rate and extent of absorption by various routes of administration (sublingual, oral, subcutaneous, intravenous), and effect of various formulations, e.g., alum, on bioavailability.

ii. Distribution, particularly if data are available on preferential binding to a particular tissue; plasma protein binding; effect of underlying disease, if any, on distribution of extract in the body.

iii. Elimination, the relative importance of biotransformation versus renal excretion; data on body clearance; interindividual differences in clearance, and differences in clearance between children and adults.

3. Indications and usage.

a. The labeling should explicitly state each indication for use of the extract in diagnosis and therapy or both. This section must contain, for each indication, the available scientific evidence of efficacy supported by adequate and well-controlled studies as defined in 21 CFR 314.111(a)(5)(ii). If studies are still in progress, this must be indicated.

b. The limitations of the usefulness of the extract should be stated. Information concerning the degree of relief of symptoms to be expected, the length of time required before relief is effected, and duration of improvement from treatment should be provided when available. This information must be based upon adequate and well-controlled studies as defined in 21 CFR 314.111(a)(5)(ii).

c. If safety considerations are such that the extract should not be used in certain individuals, e.g., those exquisitely sensitive to the allergen in the extract, this should be stated.

d. Alternative treatment for the condition should be discussed here. Comparisons of the efficacy of extract therapy with, e.g., drug therapy, must be supported by adequate and well-controlled studies (21 CFR 314.111(a)(5)(ii)).

4. Contraindications.

The labeling must state those circumstances under which allergenic extracts should not be used because the benefit/risk ratio is too low. These circumstances might include the presence of a *significant* systemic disease, a degree of sensitivity to the allergen in question which might make the likelihood of severe systemic reactions significant, or other instances where the risk of use clearly outweighs any possible benefit.

5. Warnings.

The labeling shall state serious adverse reactions, potential safety hazards, limitations in use of extract imposed by them, and a list of measures to be taken should an adverse reaction occur. Since the administration of allergenic extracts to patients with extraordinary degrees of sensitivity may represent a genuine hazard to their well being, including the possibility of death due to anaphylaxis, a special warning box should be placed in the labeling. The warning box should include data, if available, on the frequency of serious adverse reactions, the approximate mortality and morbidity rates, if known, and recommendations for the emergency management of adverse reactions. It would be appropriate to indicate in the box that allergenic extracts should not be administered in any setting in which the capability of coping with anaphylaxis does not exist, and a step-by-step outline of treatment of anaphylaxis would be appropriately included within this warning box.

6. Precautions.

a. General information in this section should include details of any special care to be exercised by the physician for the appropriate use of the allergenic extract.

b. Information to be provided the patient concerning the allergenic extract should be stated. For example, it would be appropriate that the patient be instructed to observe the extent of a local reaction and, of course, report any evidence of a late systemic reaction.

c. Any evidence of carcinogenic or mutagenic properties of the allergenic extract should be included in this section. The labeling shall state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species in which the experiments were done and the results should be stated. Data on reproductive studies and impairment of fertility, if any, should be included.

d. The allergenic extract should be categorized in terms of pregnancy categories in accordance with FDA regulations.

7. Adverse reactions.

All adverse reactions known to be associated with the use of allergenic extracts should be included in this section. Adverse reactions should be listed by organ system, by severity of reaction, by frequency, and my

mechanism if known. As noted above, potentially fatal adverse reactions should be noted in the "warning" section of the labeling.

8. Overdosage.

The labeling shall describe the signs and symptoms of overdosage of allergenic extract. Specific information on the emergency treatment of the overdosage reaction should be provided in greater detail than that which was provided in the "Warnings" box.

9. Dosage and administration.

It would be appropriate to include recommendations concerning an average typical immunotherapy regimen and any modification of the regimen because of the degree of sensitiveity of the patient or in patients with a particular problem such as disease or pregnancy. It may be helpful to include a specific table illustrating a hyposensitization regimen. Directions on dilution, preparation and administration of allergenic extracts should be included. Storage conditions for preservation of activity of the allergenic extract should be provided.

10. How supplied.

This section of the labeling shall include information on the various forms in which allergenic extracts are supplied, for exalmple, aqueous, glycerinated, aluminum adjuvants, lyophilized or other modifications of the extract.

The Panel has written two suggested package inserts exemplifying the type of required information. These are intended as guidelines for the development of package inserts for specific allergenic extracts where scientific information is available as opposed to labeling for package inserts which apply to a group of like substances.

Example of Labeling for Short Ragweed Pollen Extract

1. Description.

a. Short ragweed Pollen extract, aqueous.

b. Solution for administration by cutaneous (scratch or puncture), intracutaneous injections, or aerosol inhalation for diagnostic purposes, and for subcutaneous injection for treatment purposes.

c. Contains an aqueous extract of short ragweed pollen, soldium chloride and sodium bicarbonate, glycerin (50 percent), and phenol (0.4) percent.

d. Product is sterile.

e. Allergenic extract.

f. pH 7.4.

2. Clinical pharmacology.

a. After introduction of ragweed allergen into the skin of a ragweed-sensitive individual, the following sequence of events is known to occur. Ragweed-antigen molecules interact with ragweed-specific IgE antibody molecules bound to the surface of the mast cell. This leads to liberation of histamine and other biologically-active substances from the mast cell. This histamine acts on small blood vessels in the skin, producing increased permeability and dilation. The net result is a wheal and flare, which constitutes the positive skin test. It should be recognized that improper technique or the use of test solutions that are two concentrated or contain irritant substances may cause histamine release and a wheal and flare skin reaction by a toxic nonimmunologic pathway.

b. The following immunologic changes have been observed in patients receiving ragweed immunotherapy:

(1) *Humoral changes.* (a) Following the increase in ragweed IgE antibody that occurs during the first few months of therapy, specific (ragweed) IgE decreases after long-term treatment with ragweed extract. (b) The anticipated seasonal rise in specific (ragweed) IgE antibody is suppressed. (c) IgG ragweed antibodies of the antigen binding or "blocking" type are increased significantly beyond that commonly found in untreated patients, and the increment is dose related. The titer of ragweed IgG antibody slowly decreases over a number of months following discontinuation of therapy.

(2) *Cellular changes.* (a) Basophil cell sensitivity as assessed by ragweed antigen E-induced histamine release is usually decreased. (b) Over the course of time, the skin test reaction may diminish in size, presumably resulting from decrease in mast cell-bound IgE-specific ragweed antibodies. This may occur spontaneously or as a result of treatment.

3. Indications and usage.

a. Short ragweed-pollen extract is used in the diagnosis of IgE mediated allergic disorders such as hay fever and asthma due to exposure to ragweed pollen. Short ragweed pollen extract is administered for perennial or preseasonal immunotherapy of allergic disorders such as hay fever and asthma caused by short ragweed pollen.

b. Carefully controlled studies of the efficacy of ragweed extract administration for the long-term control of symptoms of ragweed hay fever have been carried out in a relatively small number of adults and in an even smaller number of children. The patients studied were, as a group, considered to be those with more severe symptoms of the disease. The evidence shows that some, but not all, patients with ragweed hay fever receive a degree of benefit from the administration of potent ragweed pollen extract. It is not evident how many patients in the reported studies receive sufficient clinical benefit from the treatment to enable them to discontinue drug therapy. Moreover, how often the treatment is associated with a permanent cure of the disease is not known. The value of ragweed pollen extract in the treatment of asthma due to IgE-mediated allergy to ragweed pollen has not been established by adequately designed studies. However, clinical experience supports the efficacy of ragweed pollen extract in treatment of ragweed pollen induced asthma.

c. The immunologic changes which result from immunotherapy with short ragweed pollen extract (described in Section 2) do not occur as the result of drug therapy alone.

In patients with mild degrees of symptoms of short ragweed-pollen hay fever, adequate relief may be obtained with oral antihistamines and decongestants alone. Topically applied systemic corticosteroids provide very effective relief of symptoms in many patients with ragweed hay fever. However, the possible adverse effects of corticosteroids must be considered, but are thought to be clinically insignificant for short-term use in the low doses usually required for relief of hay fever symptoms.

4. Contraindications.

Ragweed pollen extract should not be administered in the presence of a disease which makes parenteral injections hazardous such as a bleeding diathesis.

5. Warning: May cause anaphylaxis; see precautions below. Children with nephrotic syndrome require careful consideration as candidates for injection therapy since a variety of seemingly unrelated events such as routine immunization can cause an exacerbation of their nephrotic disease.

6. Precautions.

a. The possibility of the occurrence of anaphylaxis is the major adverse effect of skin testing with ragweed extract. The risk can be minimized by taking a careful history and testing initially by the cutaneous (puncture or scratch) method or with the use of dilute extracts if the intracutaneous method is employed. Anaphylaxis is also the major adverse effect of ragweed extract administration to clinically sensitive patients. The risk can be minimized by adherence to a careful injection schedule, which starts with low concentrations of extract and is increased slowly. The physician must be prepared to treat anaphylaxis should it occur and have the necessary drugs and

equipment on hand to do so. Since the most serious reactions following ragweed extract administration occur within 20 minutes of the injection, the patient should remain under observation for this period of time. The size of the maximum local reaction should be recorded since increasing large local reactions may precede a subsequent systemic reaction with increasing dosage. However, it should be noted that occasionally a systemic reaction may occur in the absence of a preceding local reaction.

b. Extracts should not be administered by the patient or other individuals who are not prepared to treat anaphylaxis should it occur.

c. Because of the possibility of an anaphylactic reaction to the injection of allergenic extract, the patient should remain in the physician's office for at least 20 minutes after the injection is administered. Any unusual reactions to the extract should be brought to the attention of the physician. In particular, this includes unusual swelling and/or tenderness at the injection site or reactions such as generalized skin itching, hives, swelling of the eyes, rhinorrhea, sneezing, coughing, wheezing, shortness of breath, nausea, dizziness, or faintness. Any other reaction occurring in such a time relationship to the injection as to suggest cause and effect should be discussed with the physician.

d. There is no evidence of carcinogenicity of short ragweed-pollen extract. No long term studies in animals have been performed to evaluate carcinogenic potential.

e. Pregnancy. Category C. Adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. There are insufficient well-controlled studies in pregnant women, but investigational experience does not include any positive evidence of adverse effects on the fetus. Allergenic extracts should be used in pregnant women only when clearly needed. Caution should be exercised in testing or treating the pregnant female because a systemic reaction may cause an abortion as a result of uterine smooth muscle contractions.

7. Adverse reactions.

Adverse reactions usually occur within minutes after an injection or skin test and consist primarily of allergenic symptoms such as generalized skin erythema, urticaria, pruritus, angioedema, rhinitis, wheezing, laryngeal edema, and hypotension. Less commonly, nausea, emesis, abdominal cramps, diarrhea, and uterine contractions may occur. Severe reactions may cause shock and loss of consciousness. Rare fatalities have occurred.

Systemic reactions occur with varying frequency, usually following less than one 1 percent of injection treatments. To some extent, the reaction rate is related to the type and dose of administered extract and to the degree of sensitivity of the patient. Despite all precautions, occasional reactions are probably unavoidable.

There is no documentation of other adverse reactions directly resulting from long-term immunotherapy.

Therapy of systemic allergic reactions is somewhat dependent upon the symptom complex. Epinephrine hydrochloride 1:1000, aqueous, in an adult dose of 0.3 to 0.5 mL (or 0.01 mL per kilogram for children) administered subcutaneously in the opposite arm is the immediate treatment of choice. A tourniquet should be placed above the site of the extract injection if the test was done on the extremities. Antihistamines may offer relief of recurrent urticaria and associated skin reactions and gastrointestinal symptoms. Persistent wheezing may necessitate intravenous aminophylline treatment. For profound shock and hypotension, intravenous fluids, vasopressors, and oxygen may also be needed. Maintenance of an open airway is critical if upper airway edema is present. Corticosteroids are not considered therapy of immediate choice but may provide benefit if symptoms are prolonged or recurrent.

Local reactions consisting of erythema, itching, swelling, tenderness and sometimes pain may occur at the injection site. These reactions may appear within a few minutes to hours and persist for several days. Local cold applications and oral antihistamines may be effective treatment. For marked and prolonged local reaction, steroids may be helpful.

Injection of ragweed extract into nonatopic volunteers has been reported to cause the appearance of IgE anti-ragweed antibody (in addition to IgG & IgM).

8. Overdosage.

The signs and symptoms of overdosage are those of excessive swelling or systemic anaphylaxis and are discussed under "Adverse Reactions."

9. Dosage and administration.

a. Recommended usual dose.

i. Diagnosis. For scratch and puncture tests, the usual testing concentration is 1:20 w/v, 100 microgram antigen E/mL or 10,000 PNU/mL. For intradermal testing, the initial test should be performed with dilute solutions, usually in the range of 1:20,000 w/v, 0.1 microgram antigen E/ML or 10 PNU/mL or less. A dose of 0.02 mL of extract is injected intradermally with a 26 or 27 gauge short bevel needle on the forearm or upper outer aspect of the arm. If no reaction occurs, the testing may be repeated with an approximate 10 to 100 fold stronger concentration. Nonimmunologic (irritative) reactions may occur with higher concentrates. This will vary with the individual extract. Physicians should be aware of the concentrations which will elicit positive reactions in allergic individuals and irritative reactions in nonallergic individuals. Skin tests are graded in terms of the wheal and erythema response noted at 10 to 20 minutes. Wheal and erythema size are best recorded by actual measurement of the extent of both responses. Some physicians use an arbitrary 1+ to 4+ scale (4+ being the largest) to grade the reactions.

Antihistamines can significantly inhibit the immediate skin test reaction. This effect has been primarily documented when testing was performed within 1 to 2 hours after antihistamine ingestion. However, partial inhibition of the skin test reaction has been observed up to 7 days after discontinuation of daily antihistamine therapy. Hydroxyzine, in particular, may cause prolonged inhibition. Epinephrine inhibits the immediate skin test reactions for several hours.

ii. Therapy. A recommendation for the usual dose cannot be made. Dosage of allergenic extract is a highly individualized matter and varies significantly according to the degree of sensitivity of the patient and his/her clinical response and tolerance to doses of allergenic extract administered during the early phases of an injection regimen. In practice, the initial dose of allergenic extract is based upon the patient's clinical and skin test sensitivity. In patients who appear to be exquisitely sensitive by history and skin test, the initial dose of the extract should be very small. The amount of allergenic extract is increased at each injection by no more than 50 percent of the previous amount, and the next increment is governed by the response to the last injection. Large, local reactions which persist for longer than 24 hours are generally considered an indication for repetition of the previous dose without increasing for reducing the dose. Any evidence of systemic reaction is an indication for a significant reduction (at

least 50 percent) in the subsequent dose. The upper limits of dosage has not been established; however, doses above 10,000 protein-nitrogen units/dose or 1 mL 1:20 w/v are rarely administered. Dosage of allergenic extract does not vary significantly with the respiratory allergic disease under treatment. The optimal interval between doses has not been definitively established. However, as is customarily practiced, injections are given initially 1 to 2 times per week with a gradual lengthening of the interval between injections after the maintenance dose of extract is reached. At this time, the injection interval is increased to 2 weeks, then subsequently to 3 weeks, and then to 4-week intervals. If the patient's clinical response is satisfactory, a 4-week interval between injections may be continued. It is not considered advisable to extend the interval between doses beyond 4 weeks without decreasing the subsequent dose. The dosage of an individual injection and the interval between injections may need to be modified during the pollen season according to the clinical response of the patient.

The usual duration of treatment has not been established. A period of 3 years of injection therapy constitutes an average minimum course of treatment.

Children and geriatric age patients appear to tolerate allergenic injections will, and no special recommendations need to be made for this group.

Extract is administered with a 1 cc. tuberculin-type syringe and a 25- or 26-gauge needle subcutaneously in the triceps region, low enough to permit application of a tourniquet above the injection site if necessary. Volumes greater than 1 cc are not injected in one site. Allergenic extracts should be stored at 2 to 8 °C to preserve their activity.

10. How supplied. (Information for the specific product.)

Example of Labeling for Codfish Extract

1. Description.

a. Codfish extract, aqueous.

b. Solution for administration by cutaneous (scratch or puncture), intracutaneous injection for diagnostic purposes.

c. Contains an extract of cod white muscle myogen, sodium chloride and sodium bicarbonate, glycerin (50 percent), and phenol (0.4 percent).

d. Product is sterile.

e. Allergenic extract.

f. pH 7.4.

2. Clinical pharmacology.

a. After introduction of codfish into the skin of a codfish sensitive individual, the following sequence of events is known to occur. Codfish antigen molecules interact with codfish specific IgE antibody molecules bound to the surface of the mast cell, which leads to liberation of histamine and other biologically active substances from the mast cell. The histamine acts on small blood vessels in the skin, producing increased permeability and dilatation. The net result is a wheal and flare, which constitutes the positive skin test. It should be recognized that improper technique or the use of test solutions that are too concentrated or contain irritant substances may cause histamine release and a wheal and flare skin reaction by a toxic nonimmunologic pathway.

3. Indications and usage.

Codfish extract is used in the diagnosis of IgE-mediated allergic disorders of the skin, gastrointestinal, and respiratory tracts. There is limited evidence to show that codfish extract is not effective by oral or parenteral administration in the treatment of IgE mediated disease.

4. Contraindications. None.

5. Warning. May cause anaphylaxis, see precautions below.

6. Precautions. Codfish extract should be used with care in testing individuals who are known to have anaphylactic sensitivity to codfish.

a. The possibility of the occurence of anaphylaxis is the major adverse effect of skin testing with codfish extract. The risk can be minimized by taking a careful history and testing initially by the puncture or scratch cutaneous method or with the use of dilute extracts if the intracutaneous method is employed.

b. Codfish extract for skin testing must not be administered unless facilities for treatment of anaphylaxis are available.

c. There is no evidence of carcinogenicity of codfish extract. No long-term studies in animals have been performed to evaluate carcinogenic potential.

d. Pregnancy. Category C. Adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. There are no well-controlled studies in pregnant women, but investigational experience does not include any positive evidence of adverse effects on the fetus. Caution should be experienced in testing the pregnant female because a systemic reaction may include uterine smooth muscle contractions.

7. Adverse reactions.

Adverse reactions usually occur within minutes after a skin test and consist primarily of allergic symtoms such as generalized skin erythema, urticaria, pruritus, angioedema, rhinitis, wheezing, laryngeal edema, and hypotension. Less commonly, nausea, emesis, abdominal cramps, diarrhea, and uterine contractions may occur. Severe reactions may cause shock and loss of consciousness. The incidence of systemic reactions following skin testing with codfish extract is unknown.

The incidence of systemic allergic reactions is related to the concentration of extract used for skin testing and the method. Puncture testing is less likely to cause a systemic reaction than is intracutaneous testing unless properly diluted extracts are used in the latter method. The degree of sensitivity of the patient is an important factor.

Despite all precautions, occasional reactions are probably unavoidable. The very sensitive patient will almost immedately note itching at the site of the test. If a puncture test is done, the extract should be immediately wiped away. Therapy of systemic allergenic reactions is somewhat dependent upon the symptom complex. Epinephrine hydrochloride 1:1000, aqueous, in an adult dose of 0.3 to 0.5 mL. (or 0.01 mL per kg for children) administered subcutaneously in the opposite arm is the immediate treatment of choice. If the test was done on the extremities a tourniquet should be placed above the site of the skin test. Antihistamines may offer relief of recurrent urticaria and associated skin reactions and gastrointestinal symptoms. Persistent wheezing may necessitate intravenous aminophylline treatment. For profound shock and hypotension, intravenous fluids, vasopressors, and oxygen may also be needed. Maintenance of an open airway is critical if upper airway edema is present. Corticosteroids are ineffective in the control of immediate reactions, buy may provide benefit if prolonged or recurrent symptoms are anticipated.

Local reactions consisting of swelling, itching, and erythema may persist at the skin test site. Local cold applications and oral antihistamines may be effective treatment. Topical corticosteroids may be useful.

8. Overdosage.

The signs and symptoms of overdosage are those of anaphylaxis and are discussed in Section 7.

9. Dosage and administration.

a. Recommended usual dose. For scratch and puncture tests, the usual testing concentration is 1:20 w/v or 10,000 PNU/mL. For intradermal testing, the initial test should be performed with dilute concentrates, usually in the range

of 1:20,000 w/v or 10 PNU/mL or less. A dose of 0.02 mL of extract is injected intradermally with a 26 or 27 gauge short bevel needle on the forearm or upper outer aspect of the arm. If no reaction occurs, the testing may be repeated with an approximate 10- to 100-fold stronger concentration. Nonimmunologic (irritative) reactions may occur with higher concentrates. This will vary with the individual extract. Physicians should be aware of the concentrations which will elicit no positive reactions in allergic individuals and irritative reactions in nonallergic individuals. Skin tests are graded in terms of the wheal and erythema response noted at 10 to 20 minutes. Wheal and erythema size are best recorded by actual measurement of the extent of both responses. Some physicians use an arbitrary 1+ to 4+ scale (4+ being the largest) to grade the reactions.

Antihistamines can significantly inhibit the immediate skin test reaction. This effect has been primarily documented when testing was performed within 1 to 2 hours after antihistamine ingestion. However, partial inhibition of the skin test reaction has been observed up to 7 days after discontinuation of daily antihistamine therapy. Hydroxyzine, in particular, may cause prolonged inhibition. Epinephrine inhibits the immediate skin test reactions for several hours.

10. How supplied. (Information on the specific product.)

2. *Container label recommendations.* Labeling standards for each container of an allergenic extract are specified in 21 CFR 610.60. These include:

1. The proper name of the product.

2. The name, address and license number of the manufacturer.

3. The lot number or other lot identification.

4. The expiration date.

In addition, the Panel recommends the following information on all container labels:

5. Strength of the extract.

6. "Recommended dose: See package insert."

7. Preservative and its concentration.

8. Storage conditions.

9. "Precautions: See package insert. May cause serious adverse reactions. All doses to be administered under supervision of a physician."

3. *Package label recommendations.* Labeling standards for each package containing an allergen extract product are specified in 21 CFR 610.61. These include:

1. The proper name of the product.

2. The name, address, and license number of the manufacturer.

3. The lot number or other lot identification.

4. The expiration date.

5. The preservative used and its concentration or if no preservative is used and the absence is a safety factor the words "no preservative."

6. Volume and strength of extract.

7. Storage conditions.

8. Statement "No U.S. Standard of Potency" when none exists.

In addition, the Panel recommends the following information on all package lables:

9. "Precautions: See package insert. May cause serious adverse reactions. All doses to be administered under the supervision of a physician."

10. "Recommended dose: See package insert."

11. "Route of administration: See package insert."

4. *Promotional material and other labeling recommendations.* There are three somewhat interrelated areas of allergy practice, in which allergenic extract manufacturing companies have provided the physician with specific guidelines for patient diagnosis and treatment. The Panel believes that the companies should have no direct responsibility which may be construed as engaging in the practice of medicine. These areas of concern are (1) formulation of diagnostic kits; (2) determination of the formula of individual patient therapeutic extract mixtures; and (3) preparation of specific dose schedules for therapeutic extracts.

a. *Diagnostic kits.* Diagnostic allergenic extract sets are offered by some manufacturers. These are intended to provide the physician with the necessary testing allergens for patients with seasonal or perennial problems in specific regions of the country. In addition, specialty sets, such as insect extracts, are also available. It should be expected that a physician entering any phase of allergy practice would have some degree of training and competence and some knowledge of the materials required for reliable diagnostic testing. The allergen manufacturing company should be allowed to give suggestions and advice but regional and specialty diagnostic set contents should be based only on reliable data. The physician should be responsible for selecting and administering only the specific desired extracts and performing tests with the appropriate extract concentration and the labeling issued by the manufacturer should not be misleading by improper suggestions based upon the kit contents, i.e., more extracts in kits than necessary to test.

b. *Individual patient therapeutic extract mixtures.* It has been common practice to use diagnostic skin test results as a basis for the preparation of therapeutic extract mixtures. Manufacturers have been reported to sometimes make the major decisions regarding the formulation of the therapeutic extract (amount and type of each allergen) after receiving reports of the skin test results, with or without supportive clinical information. The Panel believes that the manufacturer should not engage in medical practice. The responsibility for the therapeutic allergenic extract formulation belongs to the patient's physician.

The Panel strongly believes that good medical practice is best conducted by physicians, including allergists, who personally perform or supervise the history and physical examination, which are the fundamental investigative procedures, and who personally supervise further diagnostic and therapeutic procedures.

The Panel is concerned about labeling which encourages the use of allergy skin tests or in vitro assays of specific IgE as the sole basis for formulating allergenic extracts for immunotherapy. Such practices have reportedly been conducted in conjunction with allergenic extract suppliers by some physicians who have not had direct personal contact with the patient.

The validity of laboratory procedures which may be useful in investigating possible allergic disorders, such as allergy skin tests and radioallergosorbent tests (RAST) is based not only upon the proper technical performance of these tests, but also on their clinical interpretation. The necessity for evaluating the results of such tests within the context of the detailed historical information and the patient's physical status cannot be over emphasized. Consequently, the indirect or remote direction of allergy investigation or therapy is considered extremely poor medical practice. The Panel wishes to discourage labeling which promotes allergy skin tests or in vitro assays of specific IgE as the sole basis for formulating allergenic extracts for immunotherapy.

c. *Specific dose schedules for therapeutic extracts.* Therapeutic extracts are often provided by the manufacturer with labeling which includes "standardized" dose schedules. The problems of a specific therapeutic dose schedule has been discussed in other parts of this document.

There is no established dose of allergenic extract prior to treatment for any patient. It is necessary to establish

tolerance by starting with a safe, low dose, and increasing the dose at regular intervals to a maintenance level appropriate for that patient. There is a wide variation in these requirements, which is not based on age, weight, or any factor other than the degree of sensitivity of the patient and his response to the extract. A physician employing allergenic extracts in diagnosis and treatment should be familiar with their use through training and experience and should determine the therapeutic dose schedule.

In conclusion, the Panel does not wish to imply that the treatment of allergic diseases with allergenic extracts should be restricted to those physicians with formal training in allergy or immunology and/or board certification. Neither should a company producing extracts imply in promotional material that use of a kit by a physician, plus support and advice from the company which sells the kit, will fulfill the requirements for the proper treatment of allergic diseases. The company should not be required to check the credentials of a physician who orders products from it; but, on the other hand, the company should not be engaged in the recruitment of untrained physician users through advertising with offers to train them by mail as this may lead to overuse or misuse of extracts.

At the same time, the company should be free to make supported statements on the quality, efficacy, safety, etc., of its products in order to encourage physicians to use them. The company should be free to publish factual information on the practice of allergy, conduct workshops, sponsor instructional courses, and other similar activities normally used in the ethical promotion of diagnostic and therapeutic agents.

References

(1) **Federal Register** 40 FR 15392, 1975.
(2) **Federal Register** 44 FR 37434, 1979.

G. Fixed Combination Allergenic Extracts

This statement specifically refers to those fixed allergen mixtures formulated by the manufacturer. The same principles should also apply to mixtures of allergens prepared by the individual physician or by the manufacturer for an individual patient upon prescription by a physician.

The use of fixed combinations of allergenic extracts for both diagnosis and therapy has been common practice for many years. Combining extracts for diagnostic purposes has been found to be useful in testing certain patients for skin sensitivity and minimizes the need for individual tests. The use of combinations has been particularly common in skin testing children in order to minimize the number of tests. The skin testing portion of the evaluation may be expeditiously accomplished if the patient is "screened" by testing with a combined extract. If the skin test is negative, further testing with the individual components is generally not indicated, unless the resuts are incompatible with the patient's history. For example, in testing with a tree pollen extract mixture, if the skin test reaction is negative in the face of a good clinical history of allergy due to one component, the patient should be tested with the extracts of individual tree pollens. If a positive result with the mixture is obtained, components of the extract must be tested individually to whether sensitivity to one or all of the components exists. Properly employed extract combinations for testing should result in saving time and money for the patient and the allergist.

There are disadvantages to skin testing with a combined extract. If too many individual components are present in the combination, sensitivity to an antigenic determinant of one component may not be ditected because of low concentration. On the other hand, if the patient is exquisitely sensitive to several of the components of a mixture, or if the patient is sensitive to an allergen common to several components (as with grasses), a constitutional reaction may be precipitated in the course of skin testing. The latter would have most likely been avoided had the extracts been tested individually.

In allergenic extract treatment programs, combinations have been widely used to decrease the number of individual injections required for a patient with multiple sensitivities. The practical disadvantages of using combinations of extracts in therapy are of a similar nature to those described for skin testing. If a large local or systemic reaction occurs during the course of injection therapy with a combination extract, there is no way of determining which of the components is responsible for the adverse reaction without testing them individually. Inclusion of an allergen to which a patient is very sensitive as a component of a mixture may limit the amount of other allergens which can be injected because of reactions due to the one component. On the other hand, if too many (arbitrarily defined by the Panel as no more than 5 to 10) different allergens are combined in a "mix", it may not be possible to achieve an adequate dosage of any one in a volume (no more that 1 mL which is acceptable for injection at a single site. Since studies of effectiveness in the ragweed system have reported a relationship between dosage and clinical improvement (high-dosage regimens produce better results than low-dosage regimens), a mixture with too many components would not be expected to give optimal results because of a diluting effect of each component on the others. An additional disadvantage of using a combination of extracts in therapy is a possibility of inducing sensitivity in the patient to a component of the mixture to which he/she was nonreactive before therapy. The likelihood of this occurring to a degree which would have clinical significance is largely conjectural, but there are data from at least one investigation (Ref. 1) which indicate the stimulation of IgE antibody in normal individuals injected with allergenic extracts.

Another undesirable feature of the use of combinations in therapy relates to a phenomenon known as antigenic competition. Antigenic competition may be defined as "the inhibition of the immune response to one antigen or antigenic determinant which is caused by the administration of another antigen or antigenic determinant". Although the phenomenon has not been studied in the human in relation to either immunizing agents commonly used for prevention of disease or in allergy immunotherapy, the phenomenon has been clearly demonstrated in animals (Refs. 2 and 3) and is of potential significance in man when mixtures of allergens are injected simultaneously. Enhancement of the immune response by injection of combinations of allergens has not been documented.

Usually, extracts of only a single botanical or generic class are combined, but unrelated as well as related mixtures are offered. There are extract mixtures of tree, grass and weed pollens, smuts, molds, animal epidermals, household inhalants, dusts, insects, and foods. In addition, regional mixtures such as Eastern tree mix, coastal tree mix, Western weed mix, inland weed mix, etc., are available. The practice of combining extracts of common antigenic character for either diagnosis or therapy is unnecessary if the two components possess identical antigenic determinants. Testing and treatment in this instance with one allergen would suffice, as is the case with certain members of the grass family which possess common determinants insofar as stimulation of IgE antibody is concerned.

Based upon the above considerations, the Panel has concluded the following:

1. *Mixtures for skin test diagnosis.* a. The combination of extracts for

diagnostic purposes in allergy skin testing is an acceptable procedure. Fixed combination extracts, standardized for each component, used in this manner may be placed in regulatory categories corresponding to the categories of the individul components.

b. Labeling of combination products for diagnosis should include instructions for interpretation of the tests, and cautions about excessive reactions, particularly in individuals who may be sensitive to more than one component of the mixture.

c. Inclusion of excessive numbers of components in a combination should be avoided. The Panel considers more than 5 to 10 components to be excessive.

2. *Mixtures for immunotherapy.* a. The use of combination extracts for therapy is acceptable practice providing it can be assured that the patient receives only those allergens to which he/she is clinically sensitive. Regulations [21 CFR 601.25(d)(4)] specify that each entity in a combination product shall make a contribution to the claimed effects in the patient.

b. When more than one component is included in a product the amount of each must be sufficient to ensure that an adequate dose of each component can be given to the patient.

c. The labeling should note that the occurrence of excessive local reactions or systemic reactions to a combination product must be investigated to determine which component of the extract is responsible for the adverse effect.

d. Labeling for therapy should include cautions that the patient should not receive extracts of a substance to which he/she is neither reactive on skin testing nor clinically sensitive. Standard mixtures are not recommended for immunotherapy.

e. Labeling of all combination products should alert the physician to the possibility that the patient may become sensitized to components of the mixture to which he/she was not previously sensitive.

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H. Standardization and Establishment of Potency of Allergenic Extracts

1. *Introduction.* Standardization means the demonstration that the quality of allergenic extracts is comparable to that of appropriate reference preparations which have been designed as standards. Potency is defined in 21 CFR 600.3(s) as follows: "The word 'potency' is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adquately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result." Effective standardization of the content of an allergenic extract does not necessarily guarantee its potency.

Most allergenic extracts are heterogeneous mixtures of which the active allergens are only a small portion of the total mixture. The remainder of various proteins (including enzymes), other nitrogen-containing substances, carbohydrates, and other ill-defined substances, some of which may interfere with in vivo and in vitro testing of potency. For use in diagnosis and therapy, allergenic extracts should contain mainly allergens and the lowest possible amount of irrelevant substances, particularly those which can create immunologic or nonimmunologic complications. Still, the requirements for purity, standarization, and potency testing must not be so strict,that production is no longer feasible (Ref. 1).

With only a few exceptions, the contents of currently available allergenic extracts are not standardized, and their potency is not established. In this respect, they differ from the majority of diagnostic agents and drugs available in medical practice. Most allergenic extracts are simply identified by the taxonomic classification of the source material from which they are derived. Reference preparations, of which only a few are presently available, are not otherwise used by manufacturers to produce extracts of consistent quality. Estimation of the potency of allergenic extracts usually has been based upon the initial weight of the extracted source material or upon the protein nitrogen content of the final product. Although these two designations have gained wide acceptance, neither has proved to be a reliable index of potency. The increasing ability to define complex biological materials has made it apparent that these techniques provide inadequate information about composition or potency of allergenic extracts. Proof should be expected that the biologically active ingredients claimed to be in a biological product are in fact present. Active ingredients of allergenic extracts should be identified as precisely as is consistent with current knowledge and a quantitative estimate of their concentration should be provided.

Allergenic extracts must be safe. They must also be effective. Effectiveness depends on established potency. Consequently, the measurement of potency is second only to safety as a mandatory attribute of allergenic extracts and must precede attempts to determine effectiveness. Because there is no suitable animal model for human allergic diseases, it is necessary to demonstrate their effectiveness in man, i.e., in patients who suffer from diseases inducted by the active components of the extract.

Allergenic extracts are used for diagnosis and therapy. It is comparatively easy to detect potency in an extract for diagnosis in which the active ingredient(s) interact in a demonstrable way with specific IgE antibody. In therapy, the function of the active ingredient(s) is still not known, although they appear to diminish the amount of IgE antibody attached to sensitized cells, to increase the amount of "blocking" IgG antibody in body fluids or both (Ref. 2).

The potency of extracts of single source materials can be more readily evaluated than the potency of extracts of multiple, combined allergens, but ultimately the potency of allergenic extracts must be measured not only product-by-product, but also component-by-component.

2. *Approaches to standardization and the establishment of potency*— a. *Weight by volume.* The simplest and oldest means of expressing the strength of an allergenic extract is by the weight of dry allergen (i.e., source material) extracted with a given volume of fluid. Thus, an extract made by extracting 10 grams of pollen with 100 milliliters of fluid may be described as a 1:10 or 10 percent extract. This designation is not to be confused with the term "weight-to-volume" as used in chemistry where the weight in grams of a solute in a volume of solution in milliliters is expressed as a ratio. For the convenience of dealing with whole numbers rather than dilutions or fractions, the "Noon unit" or "pollen unit" has been used and is designated as the amount of material extracted from 0.001 milligram of pollen (Ref. 3).

b. *Total nitrogen.* In 1916, Cooke (Ref. 4) proposed that the measurement of total nitrogen concentration be used as a method of standardization because essentially all allergens are nitrogenous

materials. The determination of total nitrogen was gradually abandoned after introduction of the determination of protein nitrogen.

c. *Protein nitrogen.* In 1933, Cooke and Stull (Ref. 5) introduced the protein nitrogen content as a method of standardization in the belief that an albumin fraction of pollen was the allergenically active factor in the production of hay fever. Protein nitrogen represented up to two-thirds of the total nitrogen, eliminating the presumably non-allergenic nonprotein nitrogen. Extracts with a similar weight by volume ration varied greatly both in protein content and the total nitrogen content (Table I) (Ref. 5).

TABLE I.—ALKALINE SALINE FLUID EXTRACTS FROM 3 GM. DEFATTED POLLEN PER 100 C.C. EXTRACTED AND ANALYZED FEBRUARY, 1932

Pollen	Timothy			Hickory (*Hickoria glabra*)		Ragweed (*A. artemisiifolia*)	
Season collected	1921	1928	1931	1927	1931	1923	1931
Total N. (mg. per c.c.)	.21	.14	.37	.39	.41	.37	.46
Protein N. (mg. per c.c.)	.05	.06	.20	.15	.09	.09	.15
Protein N. as percent of Total N.	24	43	54	38	22	24	32

As seen in the table, extracts prepared from pollen which had been stored for different periods of time did not contain the same proportion of protein nitrogen to total nitrogen. It was also reported that when pollen extracts were diluted on a protein nitrogen basis, they compared more favorably in skin test activity (Ref. 5). The protein nitrogen content of an extract was expressed in protein nitrogen units (PNU), 1 unit being equal to 0.01 microgram of protein nitrogen (or 1 mg of protein nitrogen being equal to 100,000 PNU), after precipitation by phosphotungstic acid and measurement by the micro-Kjeldahl method. An extract prepared by extracting 5 grams of ragweed pollen with 100 mL of diluent might be described in the following ways: 5 percent or 1:20 extract, 18,000 PNU/mL, 54,000 total nitrogen units, or 50,000 Noon pollen units.

Stull et al. (Ref. 6) also found that extracts of various grass pollens, when made equal on a total nitrogen basis, were not of equal activity in direct skin tests. When diluted to be equal on a protein nitrogen basis, however, they were more nearly equal in skin test activity.

Coca (Ref. 7) disagrees with these arguments. He stated that:

1. The phosphotungstic acid-precipitable substance in pollen extracts cannot be an albumin because it is rapidly dialyzable; after it has been obtained by dialysis through a fresh collodion sac, it is found to be inert, the excitant remaining within the sac or absorbed on the membrane.

2. As has just been indicated, the separation of the nondialyzable N and dialyzable N in pollen extracts could not be confirmed.

3. The parallelism between loss of activity and loss of precipitable N could not (in the one case studied) be confirmed.

The foregoing observations deprive the proposal of Cooke and Stull of its theoretical foundation; when practically applied to the standardization of extracts of three different timothy pollen specimens, their plan was found to produce unreliable results, whereas the standardization by total N content was quite satisfactory.

Bowman (Ref. 8) found the protein nitrogen units were not reliable as a measure of potency, i.e., there was no correlation between the skin test activity of an extract and its protein nitrogen content. For example, one extract which contained 65 percent as much protein nitrogen as another extract nevertheless showed only 10 percent as much activity by skin test.

In contrast, Stull et al. (Ref. 9) stated that the drop in protein nitrogen content over a period of 2 years paralleled the loss in skin test activity.

More recently, Baer et al. (Ref. 10) examined commercial extracts of short ragweed pollen for PNU and antigen E content, as well as for reactivity in ragweed-sensitive individuals, by direct skin test and by in vitro histamine release. They found that the PNU content as labeled or as assayed in their laboratory did not correlate with either antigen E content or with the degree of biologic reactivity. There was a hundred-fold or greater difference between antigen E content of extracts labeled to have the same PNU content. At the same time, the antigen E content correlated very well with biologic reactivity.

These findings can be explained in several ways. First, most of the protein in short ragweed pollen extract, and probably in most other extracts as well, is not allergenic. Thus, PNU is not a measure of allergenically active proteins, but principally indicates the amount of allergenically inactive proteins. Second, in some extracts the most important allergens are relatively labile, e.g., antigen E of short ragweed pollen, while they constitute only a small fraction of the total protein; they may, therefore, be lost without a significant change in PNU. Third, the methods currently used to determine PNU differ from Cooke's original method and also from each other. Finally, the PNU content of an extract was sometimes not measured, but rather was calculated from the predetermined weight-by-volume value assuming that these two designations are constantly related; but this assumption is not correct (Ref. 11).

d. Measurement of allergen binding by specific IgE antibodies *in vivo;*

(1) *Direct skin test titration.* The potency of allergenic extracts can be measured by direct skin test reactivity in specifically sensitive individuals (Ref. 12). The techniques of skin testing are described elsewhere in this report and in reference 12. Estimation of the potency of an extract by this technique is complicated by (1) the lack of a generally accepted skin test procedure, (2) the different levels of sensitivity to a given extract within the patient population, and (3) the inherent variability of biological assays. Other problems in estimating potency by skin testing include the following: (4) Different skin test sites vary in their reactivity; (5) deposition of an exact volume in each skin test site is difficult; and (6) criteria for setting an end point. Regarding the latter, it is necessary to express it in terms of the dose of extract required to induce a reaction of a particular size.

In a study by Gleich et al. (Ref. 13) variation of patient sensitivity was not a problem in estimating potency. Arbesman et al. (Ref. 14), however, found considerable variability from patient to patient and suggested that patients react differently to different allergenic components in an extract. This means that a sufficiently large number of patients is necessary when using skin testing as a means to determine the potency of an allergenic extract. Some authorities recommend that at least 20 subjects should be used when testing a given extract (Ref. 15).

To improve the precision of potency estimation by direct skin testing, Aas and Belin (Ref. 16) recommend the use of intracutaneous histamine to control for the individual reactivity of each subject. They set 1 allergen unit as equivalent to 1 histamine equivalent (HE) per respective test volume when the extract elicits a specific skin test reaction of the same size as that of the appropriate histamine reference (+++), both being tested in the same manner on at least 10

individuals clinically sensitive to the actual allergen. Using this method, a close correlation between reactivity in the skin to histamine solutions and allergenic extracts has been reported (Refs. 1 and 17).

A relatively high degree of precision can be achieved in skin testing (Ref. 18). Determination of the potency of allergenic extracts by skin testing should be reproducible within a one-log variation of allergen concentration (Ref. 1).

To cite an example, the potency of short ragweed pollen extract as determined by skin test end point titration correlates well with its antigen E content and histamine releasing activity (Ref. 19) and with RAST inhibition (Ref. 13). Studies with grass pollen extracts showed a good correlation between skin reactivity and Group I allegen content; PNU content did not correlate with either of these two parameters (Ref. 20).

(2) *Passive skin transfer test.* An alternative method to direct skin testing is the passive skin transfer test of Prausnitz and Kustner (Ref. 21). This requires a pool of reaginic serum which is sterile and devoid of hepatitis antigen and also a member of normal, nonallergic volunteers as recipients. It is not likely to be used in evaluation of potency except in unusual circumstances.

e. *Measurement of allergen binding in vitro by specific IgE antibodies*—(1) *RAST based allergen assay methods.* The radioallergosorbent test (RAST) is an in vitro method which measures specific IgE antibody in serum and other body fluids (Ref. 22), and it is now widely used in many laboratories for this purpose. The method has been adapted as a means of standardization and estimation of the potency of allergenic extracts (Refs. 12, 23, and 24). Two technical approaches have been reported:

(a) *The direct RAST titration.* Serial dilutions of the allergen are coupled covalently either to paper discs or microcrystalline cellulose particles activated with cyanogen bromide. These are incubated with a serum pool containing allergen-specific IgE antibodies, and subsequently, radiolabeled antibody highly specific for human IgE is added. After another incubation period, the discs or particles are washed with buffer and the quantity of radioactivity remaining associated with them is measured in a gamma scintillation counter. Counts bound (measuring allergen) are plotted on graph paper against the various amounts of extract used in the coupling procedure and a sigmoid curve is obtained. The amount of extract required for 50 percent or maximum binding can be easily determined and compared with similar data obtained with a reference preparation tested at the same time. For example, Pepys et al. (Ref. 25) tested three commercial cockfoot pollen extracts with this method and found the same rank order of potency as measured by skin test titration.

(b) *RAST inhibition.* In this procedure, serial dilutions of the allergen extract to be tested are incubated with aliquots of a standard reaginic serum pool. After a period of incubation, discs or particles previously coupled with an optimal amount of standard allegen are added and the procedure continued as described above. The amount of extract needed to cause 50 percent inhibition of the RAST can be determined and represents a measure of the potency of that extract.

In conducting RAST assays, there are several technical aspects such as the composition of the standard serum pools and the quality of radio labeled anti-IgE and the activated paper discs or particles which are critical. The most extensive study of the reliability of RAST inhibition for the determination of the potency of allergenic extracts was carried out by Gleich it al. (Ref.13). In this study, 11 commercial extracts of short ragweed pollen were analyzed by RAST inhibition, skin test end point titration, determination of antigen E concentration, and PNU content. Potency determined by RAST inhibition showed a strong relationship to potency as measured by direct skin testing in sensitive patients. Antigen E and PNU concentrations correlated with skin test potency but less well than with RAST inhibition.

Arbesman et al. (Ref.14) also evaluated the RAST inhibition technique for determination of allergen potency. Seven different ragweed extracts were examined. No relationship was found between RAST inhibition and commonly used parameters of extract potency such as weight by volume, PNU content and total protein measurements. Intradermal skin test end point titrations were sufficiently variable in different patients that they could not be correlated with RAST inhibition results. RAST inhibition potency, however, did correlate with the antigen E content of the extract.

These studies, as well as others not mentioned here, suggest that RAST technology is a satisfactory and feasible method for standardization and measurement of the potency of at least some allergenic extracts. Lowenstein et al. (Ref. 26), however, warned that significant differences in the amino acid composition of the various allergenic components of a given extract could result in their binding to discs or particles in amounts disproportionate to their relative concentration in the extract, thus introducing a potential source of discrepancy between RAST and skin test results.

(2) *In vitro reagin neutralization.* This procedure uses the same basic principles as RAST inhibition (Ref. 27). Varying dilutions of allergen are incubated with aliquots of a reaginic serum. The mixtures are then injected intradermally into nonatopic recipients and after 24 to 48 hours the sites are challenged with a standard amount of allergen. The size of the elicited wheals and flares are determined 15 to 20 minutes later. The quantity of extracts (added to serum) which is required to cause 50 percent or maximum inhibition can then be determined. The results of in vitro reagin neutralization correlate well with RAST inhibition (Ref. 28).

(3) *In vivo reagin neutralization.* This technique involves repetitive allergen challenge of a sensitized passive transfer (P–K) site until the local reactivity is exhausted, followed by challenge with a standard or control allergen. It has been used to study the activity of fractions of ragweed pollen extract (Ref. 29).

The above two techniques are limited by the need for nonallergic recipients. The availability of the RAST makes them obsolete.

f. *Quantitation of individual allergenic components.* Quantitation of the individual components of an extract by an immunological, chemical, or physical test is an ideal method of standardization. To date, only a few allergens in a few extracts (for example, antigen E of short ragweed pollen, group I ryegrass allergen, allergen I of cat pelt, etc.) have been studied sufficiently to be assayed in this manner. While it holds great promise, this approach has several limitations which may prevent its usefulness in the near future: (1) The problem of identifying multiple allergenic fractions in the majority of extracts and of developing methods and reagents to assay each of them individually and (2) variation in the sensitivity of individual patients to the individual allergenic components in an extract.

As noted elsewhere in this report, the single most extensively studied component of any allergenic extract is antigen E of short ragweed pollen (Ref. 30). This is the major allergen in short ragweed pollen extract but it is not the only one (Refs. 31 through 33). As noted

above, the antigen E content of short ragweed pollen extract, as measured by immunoprecipitation in gel, correlates well with potency as measured by skin test end point titration (Refs. 13 and 19), RAST inhibition (Refs. 13 and 19) and histamine release activity (Ref. 14). Antigen E and PNU content do not correlate (Refs. 10 and 14) (Tables II and III).

TABLE II.—THE ANTIGEN E CONTENT AND PNU OF EXTRACTS (REF. 10)

Extract	PNU		Antigen E (mcg/mL)	PNU per mcg Antigen E	
	Claimed	Found		Claimed	Found
1	10,000	12,000	577	17	20
2	29,000	9,000	354	57	25
3	40,000	24,000	341	117	71
4	50,000	17,000	146	342	117
5	50,000	19,000	101	495	190
6	40,000	8,000	20	2,000	416

TABLE III.—INTRADERMAL END POINT TITRATION OF EACH RAGWEED EXTRACT ON ONE RAGWEED-SENSITIVE PATIENT (REF. 14)

Ragweed extract	Parameters of measurement			
	Dilution	PNU/mL	Total protein ng/mL	AgE pg/mL
1	$1{:}1.5\times10^{7}$	0.0041	0.26	28
2[1]	1×10^{6}	0.0780	2.02	220
3[1]	1×10^{5}	0.6500	16.40	370
4	1×10^{5}	0.3400	8.00	120
5	1×10^{5}	0.0620	0.80	108
6[1]	1×10^{5}	0.8400	19.30	360
7	1×10^{4}	1.7000	35.00	2,300

[1] Mixed ragweed extract.

Of the known ragweed allergens, antigen E is probably the least stable under ordinary conditions of production and storage. Accordingly, degradation of the potency of short ragweed pollen extract would be readily reflected by a change in its antigen E content. More data may be needed to support this view because there may be conditions where antigen E content would be maintained in the face of a relative lack of other allergens (e.g., lipid extraction might remove preferentially a low molecular weight allergen such as Ra–5). Similar lability of the major allergens of other extracts has not been demonstrated.

Theoretically, the potency of antigen E as a diagnostic substance could vary independently from its potency as a therapeutic agent. To elicit a wheal and flare reaction, the allergen must at least be a bivalent molecule; to alter the immune status of the individual, other molecular characteristics of the allergen may suffice. These are completely unknown at present, but bivalency may not be one of them (Refs. 34 and 37). There is at least one published study (Ref. 38) which indicates that low molecular weight fragments in timothy pollen extract may be effective therapeutically. Bivalency might not be required for RAST, i.e., a single antigenic determinant may be sufficient to bind antibody in the first stage of the RAST inhibition assay. Univalent oligopeptides derived from antigen E, perhaps formed as a result of degradation of that molecule, might be assayed as antigen E by RAST inhibition but would not react in the human skin test assay. In fact, in the latter system such oligopeptides might actually inhibit the biological activity of antigen E. Furthermore, univalent fragments are not detected by immunoprecipitation assay or by histamine release in vitro. In spite of these potential limitations, determination of the antigen E content of short ragweed pollen extracts is an accepted method for estimating the potency of these extracts.

g. *Additional methods which are used to characterize allergens or to measure their potency*—(1) *In vitro leukocyte histamine release.* Leukocyte histamine release as an in vitro analog of skin testing has been used to characterize a number of allergens and measure their potency; for example, ragweed pollen (Refs. 10 and 39), insect venoms (Ref. 40), and mouse dander (Ref. 41). Techniques of histamine release from human leukocytes are described in detail by Siraganian (Ref. 21) and by Levy (Ref. 42). To determine the potency of an allergen, various quantities of extract are added to washed leukocytes from an allergic donor, and the amount of extract needed for the release of 50 percent of the total leukocyte histamine content is determined from the dose response curve. The potency of a given extract is then estimated by comparison with the quantity of a reference preparation needed to induce the same percent histamine release. The principal advantages of this method over direct skin testing are that: (1) It avoids the possibility of anaphylactic reactions; (2) it avoids the possibility of altering the test subject's level of sensitivity to the allergen; (3) it permits the testing of antigens which have not been approved for clinical use; (4) it is significantly more precise than skin testing. The principal disadvantage is that the leukocyte histamine release method is more complex and is still mainly a research procedure. Passive leukocyte sensitization is a modification which has the advantage that it can be done with a standard reaginic serum pool and leukocytes from nonallergic donors (Ref. 42).

(2) *Single radial immunodiffusion.* A detailed description of this method is given by Davis and Ho (Ref. 43). It is now used for the measurement of the antigen E content of ragweed pollen extract and of group I allergen from grass pollens, with monospecific rabbit or goat antiserum incorporated into the gel. Standards containing known quantities of the allergen are analyzed at the same time as the unknown sample, and the quantity of allergen in the unknown is then determined by reference to the calibration curve obtained with the standard. The method depends on supplies of reference allergens (purified material is required) and monospecific antiserum. A similar method is also used to examine cross reactivity between components of different allergenic extracts.

(3) *Crossed immunoelectrophoresis (CIE) and crossed radioimmunoelectrophoresis (CRIE).* A review of the application of these methods to the analysis of allergens appeared recently (Ref. 44); details of the methods are given in several papers in the *Scandinavian Journal of Immunology*, Vol. 2, Suppl. 1, 1973. In CIE, ordinary electrophoresis in gel is followed by electrophoresis, perpendicular to the former, into an antibody-containing gel; the latter contains polyspecific antibodies against the whole allergenic extract made in rabbits or goats. The method has high resolving power and permits relative quantification of individual allergens without previous separation. In CRIE, a patient's serum containing specific IgE antibodies is flooded on the CIE gel. Then it is washed off and radiolabeled anti-IgE is flooded on the gel. Subsequent radioautography will reveal precipitates containing allergens. These procedures have been applied to the analysis of timothy pollen (Refs. 45 and 46), horse hair and dander (Refs. 26 and 47), *Cladosporium herbarum* (Ref. 48) and other allergens (Ref. 44). The main limitations to their use are the current lack of suitable antisera and the inability to recover biologically or immunologically active fractions. Nevertheless, they may prove to be acceptable alternatives to isoelectric focusing and polyacrylamide gel electrophoresis.

(4) *Polyacrylamide gel electrophoresis.* Since most allergens are proteins and proteins are electrically charged, they can be characterized by their rate of movement in an electric field. The use of gels as supporting media provides good resolution of proteins in complex mixtures. Polyacrylamide gel electrophoresis

(PAGE) is probably the most versatile and useful system for this purpose (Ref. 49). Among others, several animal dander allergens have been analyzed by PAGE (Refs. 50 and 51). By measuring the mobility in an appropriate concentration of polyacrylamide gel containing the detergent sodium dodecyl sulfate (SDS), the molecular weight of most proteins can be determined quite rapidly and simply (Ref. 52). To identify a given band in a stained gel as an allergen, an unstained gel must be sliced and the protein eluted and tested for allergenic activity by an immunological method. This is not possible when SDS is included in the gel.

(5) *Isoelectric focusing in polyacrylamide gel.* The method of separating proteins according to their isoelectric points in a pH gradient is called isoelectric focusing (Refs. 53 and 54). Birch pollen (Ref. 54), dog and cat dander (Ref. 55), horse dander (Ref. 56) and catttle dander (Ref. 57) are among a number of allergenic extracts which have been analyzed by this method. Proteins are separated as bands in the gel, and they can be eluted out and their allergenic activity assayed by skin test or by RAST. With a reference preparation, a characteristic pattern of bands can be established for each allergenic product. Nevertheless, it appears to be a highly promising test for standardization of allergenic extracts. Its usefulness depends on the ability to localize the protein bands in the gel produced by the major and minor allergens in an extract. One possible drawback is that it may not permit detection of low molecular weight allergens.

h. *Miscellaneous methods of questionable value.* Over the years, a number of methods (including nasal and bronchial provocation test, the Schultz-Dale test using sensitized monkey tissue, complement in activation and tanned cell hemaglutination) have been used to determine the activity of allergenic extracts (reviewed in Ref. 58), but the Panel finds no compelling reason to recommend their use in the standardization and potency determination of allergenic extracts.

3. *Standardization problems unique to some allergenic extracts which are used only in therapy.* Some alergenic extracts used only in therapy have been modified or combined with adjuvants which may make characterization of the final product by the above methods difficult and in some instances impossible. These extracts include:

a. Alum precipitated allergenic extracts.

b. Pyridine extracted, alum precipitated allergenic extracts.

c. Emulsified allergenic extracts.

d. Polymerized allergenic extracts (Ref. 59).

e. Formalin treated allergenic extracts.

For these extracts, determination of potency may require the development of additional techniques to insure consistency potent products from lot-to-lot. Of these five, only the first two are licensed biologicals.

4. *Conclusions.* The traditional units applied to allergenic extracts, i.e., weight-by-volume and PNU content, are not reliable measures of their biological activity and should be replaced as soon as practicable by one or more proven designations. Standardization has been considered by other groups (e.g., see Refs. 58 and 60) and remains in an active state of development. It is a matter of international concern.

Ascertaining the principal allergenic components of most extracts is technically feasible and has been accomplished for short ragweed pollen, rye and certain related grass pollens, birch pollen, cod, honey-bee venom and a few others. According to Lichtenstein (Ref. 61), the means of standardizing most allergenic extracts are well within present technical capabilities.

5. *Recommendations regarding standardization and establishment of potency.* To standardize allergenic products the following should be required:

a. Reference preparations should be developed and maintained by the Bureau of Biologics, FDA, under conditions that favor stability of their biological characteristics using such methods as lyophilization or storage in liquid nitrogen. Such primary reference standards, or secondary standards developed from them, should be made available to manufacturers of allergenic extracts and to individuals and groups engaged in research. Eventually, international standards should be adopted.

b. Biological (or immunological) activity, i.e., the ability to induce specific antibody or to react with that antibody, should be estimated by suitable in vitro or in vivo methods, in comparison with an appropriate reference preparation. Whenever possible, the contents of allergenic products should be defined in quantitative physical and chemical terms, using methods described in this document.

c. The use of standardized nomenclature in labeling, regulatory records and in articles in the scientific literature should be adopted. This would make the contents of allergenic products more readily discernible to the physician who uses them and to those persons charged with maintaining surveillance of their safety and effectiveness. All allergenic source materials (or the products thereof) that are incorporated into allergenic products should be identified in labeling in accordance with currently acceptable standard scientific nomenclature. For the present, the designations of individual products hitherto in use should parenthetically follow the definitive identification of the source of material and its species name; for example, Epithelium, *Canus domesticus* (dog dander). Because of the constraints of printing space, only the designations in current use need appear on the vial label, but the definitive name would appear in the package insert and in regulatory records supplied to the Bureau of Biologics, Food and Drug Administration. It would be expected that justification for the use of specific raw materials would be available on request.

d. Because the characterization of allergenic extracts as provided by any single test is insufficient, the following properties of all allergenic extracts should be examined when feasible:

(1) Biological activity should be determined by skin test in humans for all allergenic extracts before their first licensing in comparison with a reference. Appropriate nonimmunologic substances may be used to control for variations in individual reactivity. Skin test should also be compared with an in vitro test for the control of subsequent lots. The unit of biological activity should be based on the skin test activity. Leukocyte histamine release may be used as an alternative to skin testing.

(2) The potency of all batches of allergenic extracts should be determined by RAST inhibition, radial immunodiffusion or other methods after appropriate correlation with biological activity has been established. A minimum level of potency must be established by the Bureau of Biologics, FDA, for every allergenic extract.

(3) Identity testing of allergenic extracts by comparison with a respective reference standard should be established on all batches by isoelectric focusing in gel, crossed immunoelectrophoresis or some other reliable procedure of this general type. Minimum standards must be established by the Bureau of Biologics, FDA to ensure the availability of consistent allergenic products.

e. The possible interactions of active components in a combination product shall be evaluated as feasible to determine whether they potentiate or vitiate each others properties.

6. *Recommendations regarding future goals.* The Panel recommends that the following be adopted by all those concerned with the manufacture and use of allergenic products as goals which should ultimately be met for the standardization of allergenic extracts and establishment of their potency:

a. The allergenically active ingredients said to be present in an allergenic extract should be enumerated. This includes allergenic substances which are assumed to be present but for which proof of identity is currently either lacking or not possible.

b. A description of methods for detecting and measuring the identifiable ingredients said to be present in the allergenic product should be provided. If this is not possible, a reasonable explanation should be offered.

c. A description of methods for estimating the biological activity of each measurable ingredient, both individually and in combination, under suitably controlled conditions should be provided.

d. The methods mentioned above should be applicable to determinations of the duration of biological activities under various conditions of storage such as temperature, light, solvent, etc. The effect of incorporated preservatives and adjuvants on the activities of the components of the extract should be estimated similarly. This implies validation of the expiration date on the label, which indicates that the extract was "active" to that time.

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I. Manufacturing of Allergenic Extracts

Safety and effectiveness of allergenic extracts should be accomplished by evaluating the characteristics of the final product as it is to be used in humans. Particular attention should be given to potency determination and purity testing. There are, however, currently no appropriate potency standards or tests of composition which can be applied to all allergenic products to assure that they meet regulatory expectations. Therefore, special emphasis must be directed to the manufacturing of these products, focusing on techniques which yield a more consistent composition from lot-to-lot while at the same time avoiding methods which might potentially result in either an unsafe or an ineffective product. The Panel recommends that each manufacturer whose operations are regulated by FDA should be required to employ precisely described methods for the production of each of his licensed products. This means that each manufacturer must have detailed written procedures which implement the intent of the following recommendations.

The Panel realizes that many of the procedures involved in the production of allergenic extracts are done on a strictly empirical basis. In view of this, the Panel recommends that "established acceptance criteria" be developed by each manufacture for each of his products. "Established acceptance criteria" are the detailed production criteria which are established in the approved biological product license on file with FDA and in written standard operating procedures within the establishment. These procedures must be known and followed by all persons responsible for and involved in the manufacture of allergenic extracts. From the data submissions reviewed by this Panel, it is obvious that established acceptance criteria have not been developed for all allergenic products produced by the manufacturers.

The Panel noted that different manufacturers use different methods to accomplish the same result in production. In many instances, the value of these "unique" steps in producing a more potent or more specific product was not substantiated or documented by the producers; some of them undoubtedly result in an inferior product. The Panel recommends that the purpose for each procedure be identified and its effectiveness substantiated or justified in documentation supplied to FDA as part of the product license file and that extraction techniques be approved only if their effect on the specificity, purity, and potency of the resultant product has been shown. An example of such a technique is mechanical rupture of pollen grains before extraction. Rupturing the pollen apparently yields a product with a higher protein nitrogen unit (PNU) concentration, but it has not been shown that this increases the potency of the product. Other examples are "re-extraction" of the source material with either the same or a fresh menstruum and extraction with an alkaline pyridine menstruum.

Manufacturing Principles

The following principles were considered in developing the manufacturing recommendations:

1. *Purity.* An allergenic product should contain allergens derived from the source material named on the label and should not contain allergens from other source materials in amounts sufficient to be detected by skin tests or *in vitro* tests. The extract should not contain extraneous microorganisms or harmful toxic substances derived from microoganisms. This will require proper collection, identification, and processing

of the source material and extracts made therefrom.

2. *Potency.* Each allergenic product should contain an amount of specific allergenic activity related to the potency statement on the label. Standardization of allergenic extracts is discussed in another section of this document.

3. *Stability.* The period of use of an allergenic product should be indicated by an expiration date on the vial. The expiration date should have been verified by appropriate testing of a reference preparation.

4. *Sterility.* Each batch of allergenic product should be sterile.

5. *Safety.* Each batch of extract should be subjected to general animal safety tests specified in FDA regulations.

Manufacturing Recommendations

In addition to the manufacturing and establishment requirements of 21 CFR Parts 210, 211, 600, and 610 and the manufacturing recommendations in this report on the various extract groups, it is recommended that the following standards shall apply to the manufacture of allergenic extracts.

1. *Source materials*—a. *Acquisition.* Source materials shall be obtained from properly qualified collectors. Reasonable measures shall be employed by the manufacturer to assure that collector qualifications and collection procedures are appropriate to verify the indentity and quality of the source material. FDA shall have inspection access to sources and collectors.

b. *Identity and purity.* Only specifically identified allergenic source materials which do not contain avoidable foreign substances shall be used in the manufacture of an allergenic product. Means of identification and limits of foreign materials shall meet established acceptance criteria for each source material. Where identity and purity cannot be determined by examination and testing of the source material, appropriate methods shall be employed to trace the material from its origin including complete identity labeling and certification from competent collectors.

c. *Processing and storage.* All steps in processing and storage of raw materials and source materials shall be performed so as to ensure that no unintended substances are introduced into the product. Measures shall be employed to minimize the introduction and growth of microorganisms. Source materials shall be used fresh or shall be stored in a manner to minimize or arrest deterioration. Source materials shall be kept only for a period not exceeding 5 years unless there are data about the specific material to support a different storage time.

2. *Operating procedures*—a. *Scope.* These recommendations are mostly covered in the production and process control requirements of 21 CFR Parts 211, 600, 610, and 680.

b. *Standard operating procedures.* Written standard operating procedures shall be maintained and shall define established acceptance criteria for each product (or product group where procedures are identical). Such written procedures shall be available to the personnel for use in the areas where the procedures are performed or otherwise located to permit access by the responsible persons. The procedures shall comply with the published requirements of the FDA regulations (21 CFR) and essential steps shall be defined in the biologic product license file as they are developed and approved. The written standard operating procedures shall include descriptions of the following:

(1) Criteria used to determine source material suitability.

(2) Methods of performing identity tests or assuring identity.

(3) Methods to assure that the source material is handled, stored and processed so as to minimize or prevent contamination with molds, bacteria, and other extraneous substances.

(4) Methods for labeling source materials.

(5) Criteria for determining the quality of the extraction solution and its components.

(6) Complete details of the production process including time and temperature restrictions for specific steps in processing.

(7) Procedures which are unique for a specific product in a group shall be clearly identified as such.

(8) All quality control tests and release limits.

(9) Procedures for packaging and labeling.

(10) Storage temperatures and systems for controlling storage temperatures.

(11) Expiration dating information for interim and final products.

(12) Retention sample procedures.

(13) Product release procedures.

(14) Shipping procedures.

(15) Criteria for handling returned products.

(16) Records preparation, verification, and retention.

3. *Tests.* The tests in 21 CFR 680.3 shall be followed.

4. *Records.* In addition to the records and reports in 21 CFR 211.180 through 211.198 and the above standard operating procedures, records and reports of studies and research which substantiate any of the firm's established acceptance criteria shall be provided as part of the biologic product license file.

5. *Stability.* Manufacturers shall employ known procedures which enhance stability. These may include the use of stabilizers, preservatives, freeze drying, optimim storage conditions and labeling precautions restricting time out of refrigeration and warnings about loss of strength when kept in high dilutions in aqueous solutions. Where potency standards are available, the expiration dating shall be verified by stability testing.

6. *Specific procedures*—a. *Composition of culture media.* Culture media into which organisms are inoculated for the manufacture of allergenic products shall contain no allergenic substances other than those necessary as a growth requirement. No animal protein nor any allergenic derivative of animal protein shall be used in culture media unless it is necessary as a growth requirement and data indicate that no significant amount of animal allergenic activity remains in the final extract.

b. *Liquid products for oral administration.* Liquid products intended for oral administration that are filled in multiple dose final containers shall contain a preservative in a concentration adequate to inhibit microbial growth.

c. *Residual pyridine.* Products for which pyridine is used in manufacturing shall have no more residual pyridine in the final product than 25 micrograms per milliliter.

d. *Vial size limits.* Final containers of sterile allergenic extracts for diagnostic use shall be no larger than sufficient to deliver 5 milliliters. Other final containers of sterile allergenic extracts shall be no larger than sufficient to deliver 30 milliliters.

e. *Epidermal extract source materials.* Source materials such as feathers, hairs, furs, pelts, skins, hides, and danders shall be free from visible traces of blood, serum and other extraneous materials. All animals from which skins and components are obtained shall be healthy prior to collecting source material or killing for collecting of source material as determined by an appropriately qualified examiner.

f. *Food extract source materials.* Food extract source materials shall be of a quality suitable for human food as defined in 21 CFR, Subchapter B, Food and Food Products, and in regulations of the Department of Agriculture. Food extract source materials shall be collected and processed in a manner to

maintain relative freedom from contaminants, including pesticides.

g. *Pollen extract source materials.* (1) Contamination with mixed pollens of other species shall not exceed 1.0 percent, or 0.5 percent with a single pollen species, as determined by microscopic count.

(2) Nonrelated contaminants: Pollen shall be relatively free of nonpollen contaminants such as leaves, earth, grit, and similar substances. Pollens unavoidably contaminated with such substances during collection shall be processed to reduce the contaminating particles not to exceed 10 percent by microscopic particle count. Extraneous particles which are separable by available physical techniques (such as sieving out substances which exceed the size of the pollen grain) shall be removed in processing.

h. *Dust extract source materials.* House dust source materials shall be collected from human dwellings employing procedures designed to exclude dwellings where animal pets, including birds, are kept unless the labeled name of the product indicates otherwise. See the discussion on house dust extracts. All dust source materials shall be processed in such a manner as to exclude gross contamination by extraneous substances.

7. *Alternative procedures.* Source materials may be collected and stored and allergenic products may be processed at variance with one or more of the requirements recommended above provided that: Data which demonstrate that such alternative procedures do not compromise the safety and effectiveness of the product is submitted and prior approval is obtained from the Director of the National Center for Drugs and Biologics and is made a part of the biological product license file.

J. Recommendations for Further Testing for Category III Allergenic Extracts

1. *Introduction.* Of the more than 1,500 allergenic extracts commercially available for diagnosis and therapy reviewed by the Panel, a small number have been generically classified in Category I (safe and effective). Another group has been generically classified in Category II or IIIB because they are unsafe, ineffective, prepared from poorly defined source materials, or because the expected risks exceed the expected benefits (e.g., castor bean). The remainder, which constitutes the bulk of the allergenic products on the market, are mostly extracts of substances known to be allergenic or highly suspect of being allergenic, but published data were either lacking or were insufficient to permit the Panel to conclude positively that these extracts are effective. These products were therefore generically classified in Category IIIA because the expected benefits versus risks do not justify revoking their licenses while they are being further studied.

Additional testing is required for all biologicals placed in Category IIIA for them to remain licensed. (In the **Federal Register** of October 5, 1982 (47 FR 44062), FDA issued new procedures for the reclassification of those biological products classified in Category IIIA). Because of the large number of allergenic extracts commercially available for diagnosis and therapy, the Panel recognizes that it is neither practical nor economically feasible for each extract to be fully tested employing adequate and well controlled human clinical studies. Therefore, more limited testing in humans for a large number of extracts is recommended and described later in this section. The cost of individually attempting to fully establish effectiveness for each extract for diagnosis and for immunotherapy for only two disorders, allergic rhinitis and asthma, in appropriately designed clinical studies could easily exceed the total yearly dollar volume of allergenic extract sales in the United States. Furthermore, many allergens, including some of those frequently used, lack the characteristics which would make the extract suitable for evaluating by means of adequate and well-controlled studies. For example, monitoring the patient's exposure to one of several concurrently occurring grass pollens or mold spores is very difficult. The Panel believes that it is quite likely that, as appropriate studies are conducted similar to those carried out with ragweed pollen extract in allergic rhinitis, many extracts in Category III will be found to be effective. For some of the most frequently used or important extracts in Category IIIA, the Panel recommends the following approaches in order that they may ultimately be qualified for Category I:

a. The manufacturers may join forces with governmental and allergy organizations to design appropriate studies, to enlist and organize the investigators, and to help support the necessary studies.

b. If experts agree on the antigenic similarity of several extracts, proof of effectiveness or ineffectiveness for one extract of a group should permit inferences by analogy to be made about the others in the group. Accepting this reasonable compromise will substantially reduce the magnitude of the testing endeavor.

c. Priorities should be established for the order in which various extracts are to be tested. one approach would be to rank extracts in the order of their volume of use or importance. Representatives from professional allergy organizations, industry, and government should be involved in the priority setting. The Panel submits the following list of extracts as suggestions for consideration for full testing by controlled clinical trials: tree pollens—oak, maple, olive, elm, pecan, mulberry, red alder and birch; grass pollens—bermuda; weed pollens—amaranth species, English plantain and Kochia; molds—*Alternaria* and *Cladosporium;* animal allergens—mouse, rat, and dog; miscellaneous—house dust and *Dermatogoides farinae;* and foods. High priority should be given to the study of the use of food extracts for therapy in the manner labeled by the manufacturer.

d. The time frame within which the testing should be conducted will depend upon the number of groups of qualified investigators and resources available. For example, with 10 groups each studying one extract each over a period of 3 years, it should be possible to fully test about 20 high priority extracts during a 6 year period.

e. More limited confirmatory studies should be performed for the remaining products as discussed below.

f. In the interest of minimizing duplicative and costly clinical testing of esentially the same drug product, which places a burden on scarce clinical testing resources without necessarily contributing to the quality of evidence required to establish an extract's effectiveness, the Panel recommends that each manufacturer should not be required to clinically test each of its own products as long as a testing plan is developed to include each product to which the same effectiveness conclusions would ultimately apply. Testing may be conducted over a period of several years involving maufacturers and/or other interested sponsors.

g. The Panel hopes that studies on all products can be completed within a period of 10 years by these or less cumbersome methods as they are developed.

h. Once the effectiveness of the generic product is demonstrated, specific company products must meet the standards of potency, specificity, and stability developed for the proven extract for their products to be placed in Category I.

2. *Recommendations for further testing of Category IIIA extracts for which complete controlled clinical studies are required to evaluate*

effectiveness and safety for diagnosis and immunotherapy. Those allergenic extracts for which complete clinical testing is recommended should first meet the following criteria:

a. The extract should have a reasonable likelihood of being allergenically active (i.e., of containing allergens).

b. There must be a reasonable likelihood that individuals are or will be exposed to the allergen in question.

c. Thee must be a reasonable likelihood that exposure to the allergen will induce symptoms and that the symptoms induced by exposure are of an allergic nature.

d. The raw material from which the extract is prepared must be clearly identified and described.

e. The manufacturing processes for preparation of the extract must conform to the usual and accepted guidelines for good manufacturing practices. These must be written and described in detail.

f. The allergenic extract product must be shown to be sterile and nontoxic by the required safety tests and to have no unanticipated adverse effects when properly used.

g. The allergens in the extract must have been standardized with a defined specificity and potency for one or more key allergenic components identified or a reference standard must be available with a reproducible composition demonstrated.

h. The product must have a demonstrated stability.

3. *Recommended procédures for developing substantial evidence of effectiveness and safety of allergenic extracts for diagnosis*—a. *General aspects*—(1) *Need.* A clinical study is deemed necessary where there is no consensus among qualified experts that the available data demonstrate that the product is effective in the diagnosis of the specific allergic hypersensitivity for which it is recommended.

(2) *Purpose.* The clinical study should be designed to determine the value of the product when used in the recommended manner as a reliable agent for assessing the presence or absence of a specific allergic hypersensitivity in comparison to or in conjunction with other available diagnostic procedures.

(3) *Protocol.* A complete detailed protocol for the conduct and analysis of the study should be prepared under the aegis of the sponsor of the study. To minimize possible conflicts in the interpretation of its results, the protocol should be reviewed with FDA before conducting the study.

(4) *Performance and conclusions.* The test should be conducted in accordance with a protocol which is mutually agreeable to the sponsor and FDA. Results obtained in clinical studies by the use of protocols not mutually agreed upon by the sponsor and FDA will not be excluded from consideration for establishing efficacy.

b. *Organization and personnel.* (1) Each person engaged in the conduct of, or who is responsible for, the supervision of a clinical study shall have the education, training, and experience to enable him/her to perform the assigned functions. There shall be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.

(2) Before the initiation of the clinical study, a professional with appropriate education, training, and experience shall be identified as the study director (principal investigator). The study director shall have ultimate responsibility for implementation of the protocol and conduct of the study.

(3) The clinical study shall be conducted in appropriate medical facilities.

c. *Testing facilities operation.* (1) The clinical study shall be conducted using a standard skin test method which is mutually agreeable to the study director and FDA.

(2) The identity, strength, quality, and purity of each batch of a test or control substance shall have been determined before the initiation of the study. The records of these analyses shall be available to the study director. Substances other than the biological materials themselves, which are contained in the test and control materials, including their amount and the method of assay, shall be identified, as well as the origin and method of preparation of the test and control substances.

(3) Where possible, the stability of each test or control substance shall have been determined by the sponsor before initiation of a clinical study unless the purpose of the study is to determine stability. If the stability of the test and control substances has not been acccurately determined before the initiation of a study, standard operating procedures shall be established and followed to ensure that its identity, strength, quality, and purity conform to specifications.

(4) Each container for a test or control substance shall be labeled with name or code number, expiration date, and appropriate storage conditions necessary to maintains its identity, strength, quality, and purity throughout the clinical study. Procedures shall be established for a system of handling the test and control substances.

d. *Protocol.* (1) Each study for the determination of the efficacy and safety of the use of allergenic extracts for diagnosis shall have an approved written protocol that clearly indicates the objectives and all methods, including statistical methods, for the conduct of the study. The protocol shall contain, but not be limited to, the following information:

(i) A descriptive title and statement of the purpose of the study.

(ii) Identification of the test and control substances by name and/or code number.

(iii) A description of the strength, quality, and purity of the test and control substances.

(iv) The name of the study director and the names of other professional persons involved.

(v) The name and address of the sponsor and the name and address of the testing facility at which the study is being conducted.

(vi) The proposed starting date and date of completion of the study.

(vii) A description of the subjects who will participate in the study with the method of recruitment of potential subjects described. The criteria for identifying subjects for inclusion in the study should be stated as specifically and as unequivocally as possible, and they should be applicable under the conditions of recommended usage. Only those indiviudals who meet the definitions of the specific hypersensitivity to be diagnosed by the use of the test substance would be included. The criteria to be applied will include the signs, symptoms and other factors considered to be most characteristic of the condition whose diagnosis is being studied. When appropriate, children may be entered into a study. The informed consent (in conformity with currently applicable governmental policy, regulation and/or law) of each participant (or legal guardian) will obtained prior to entry.

(viii) A description of the skin test procedure that will be used in the study. Complete descriptions of dosages, routes, sites, schedules, contingent modifications, and supportive, ancillary, coincidental, or other aspects of the testing procedure will be stated in the protocol.

(ix) A description of one or more independent diagnostic procedures with which the results of skin tests will be compared.

(x) An unequivocal definition of skin test responses.

(xi) A description of the statistical method that will be used in the study. It is crucial to include expert biostatistical

consultation in all phases of the clinical study, particularly in its initial design and sample size determinations.

(xii) The records to be maintained.

(xiii) All changes or revisions, and reasons therefor, to an approved protocol shall be documented, signed by the study director, dated and maintained with the protocol.

e. *Conduct of a clinical study.* (1) The study shall be conducted in accordance with the protocol.

(2) There should be two study groups, one employing allergenic individuals with symptoms,signs and other factors considered to be most characteristic of the specific hypersensitivity whose diagnosis is being studied. The other group should be composed of control individuals who are without symptoms, signs and other factors considered to be most characteristic of the specific hypersensitivity whose diagnosis is being studied. Such individuals may or may not be totally free of all known immediate hypersensitivities. The purpose of this group is to determine that test and control substances do not provoke nonspecific (i.e., irritant) reactions.

(3) Skin tests shall be done according to the following guidelines, or as otherwise agreed upon by the sponsor and the FDA, in order to minimize the known sources of variation in skin testing:

(i) Test substances shall be diluted tenfold in buffer containing a stabilizer such as 0.03 percent human serum albumin.

(ii) Only the skin of the upper part of the arms or of the back, where a large area of equal reactivity is available, shall be used.

(iii) Disposable needles and syringes shall be used to eliminate problems with residual test substance from earlier uses.

(iv) Tests to be compared shall be done at one sitting.

(v) Subjects shall take no medication which will interfere with the test 2 to 3 days prior to the test.

(vi) Equal (usually 0.02 mL) volumes of test and control solutions shall be injected. All injections shall be made intracutaneously.

(vii) Testing shall be initiated with dilutions of test solution weak enough to give a negative or trace reaction.

(viii) The smallest amount of test substance required to give a threshold (1.0 cm wheal with 2.0 to 3.0 cm erythema) response shall be considered an end point.

(ix) Testing with a control solution (the buffer solution and stabilizer used to prepare dilutions of the test substance) shall be done in every subject to determine the relative degree of nonspecific reactivity of subjects' skin.

(x) The reactivity of subjects' skin may be judged by measuring the reaction provoked by intracutaneous administration of a stated amount and concentration of a histamine solution.

(xi) Response to test and control solutions shall be graded as described by King, et al. (Ref. 1).

(xii) If negative, more concentrated solutions shall be injected until a good threshold response is obtained or until a predetermined maximum concentration is tried with no response. If, on the other hand, the initial test dilution results in a definite positive (threshold-size or greater) response, then less concentrated solutions shall be tried until a minimal positive (trace) or a negative response is obtained.

(xiii) As stated in paragraph (h) above, the smallest amount of test substance required to give a threshold response shall be considered an end point. However, when the end point appears to fall between two dilutions, the end point shall be considered intermediate between the two dilutions, and an interpolated value halfway (on a $\log_{10}$ scale) between the two dilutions shall be regarded as an end point.

(4) The effectiveness of a test substance for use in diagnosis of the specific allergic hypersensitivity for which that test substance is intended requires that the results of skin testing with the test substance be compared to one or more of the following indices of that same hypersensitivity:

(i) Clinical symptoms shall be evaluated retrospectively by means of an appropriate medical/allergy history which will be recorded on standard forms and/or prospectively by means of symptom diaries which will be filled out by study subjects for an appropriate period of time covering that period during which exposure is expected to occur. Symptom scores for each subject will be derived from the data recorded on these forms, using published methods.

(ii) Leukocyte sensitivity to the test substance can be determined by published methods.

(iii) Specific serum IgE antibody against the test substance can be determined by immunoassay (e.g., RAST).

(iv) Other methods, if approved by FDA, may also be used.

f. *Statistical analysis.* (1) To establish definitively that a test substance is effective for use as a skin test reagent in diagnosis of a specific allergic hypersensitivity, it shall be demonstrated, using the guidelines described above, that the test substance yields results that quantitatively are comparable with results obtained using clinical symptoms and one or more of the other techniques described in paragraph J.3.e.(4) above.

(2) Demonstration of comparability requires statistical analysis of the test results. Levels of significance for all tests to be employed in a study should be mutually agreed upon in advance.

g. *Safety during clinical studies of effectiveness.* Allergenic extracts intended for use in diagnosis are regarded as safe when used according to generally accepted methods, with due regard for the possibility of inducing an untoward allergic reaction. Nevertheless, the diagnostic effectivenss study may reveal unanticipated side effects and adverse clinical events. These may necessitate revision of safety standards for a specific allergenic extract. The following recommendations pertain to aspects of safety in the clinical trial.

(1) *Subjects.* There should be no unacceptable evident or anticipated levels of toxicity for subjects who meet all other criteria for entry into the clinical study of effectiveness.

(2) *Clinical observations.* Subjects enrolled in the clinical study, at entrance, shall have specified physical and laboratory evaluations as deemed necessary by the investigator and the FDA. The laboratory tests selected will be those considered appropriate for the product under study.

(3) *Continuation of study.* New patient entries into the study will be suspended if an adverse event in either study group is considered to be of sufficient importance by either the sponsor or FDA. Entries may be resumed if a consensus to continue is subsequently reestablished.

(4) *Adverse events.* In a trial which meets the conditions for initiation and continuation, two classes of adverse events will be considered:

(i) Those which are anticipated as concomitants or consequences of the test or control substances.

(ii) All others.

Events in class (4)(i) above should be specified completely in the protocol of the clinical study. Events in class (4)(ii) above may be subclassified in order of importance, e.g., sudden unexplained death, other deaths, hospitalization for illness, permanently or temporarily incapacitating events and minor signs and symptoms. The clinical study protocol must include the recording, dating and timing of all such events for each patient on a detailed standard form developed for that purpose and assigned

an importance weight and preferably mutually agreed upon by the sponsor and FDA. Analysis of adverse events during the course of the study would permit termination of the study when and if, in the judgment of the sponsor and FDA, there was evidence of an accumulation of an excess of adverse events of class (ii).

h. *Records and reports.* (1) A final report shall be prepared for each clinical study and shall accurately describe, but not necessarily be limited to, the following:

(i) Name and address of the facility performing the study and the dates on which the study was initiated and completed.

(ii) Objectives and procedures stated in the approved protocol, including any changes in the approved protocol.

(iii) Raw data generated while conducting the study and any transformations, calculations or operation performed on the data.

(iv) Statistical methods employed for analyzing the data.

(v) The test and control substances identified by name and/or code number, strength, quality, and purity.

(vi) Stability of the test and control substances under the conditions of the study.

(vii) Methods used.

(viii) Description of the study subjects.

(ix) Dosage and route of administration of the test and control substances.

(x) Name of the study director and the sponsor.

(xi) A summary of the data, an analysis of the data, and a statement of the conclusions drawn from the analysis.

(xii) The location where all raw data and the final report are to be stored.

(xiii) All raw data, documentation and other information, protocols, specimens and final reports generated during and as a result of a clinical study shall be retained. All of this material shall be made available for inspection to authorized FDA employees.

4. *Recommended procedures for developing substantial evidence of effectiveness and safety of allergenic extracts for immunotherapy*—a. *Introduction.* Well designed clinical trials are necessary for the evaluation of the effective and safety of any new biological products designed for use in therapy of disease in humans. Essentials of adequate and well-controlled clinical investigations have been previously identified (21 CFR 314.111(a)(5)(ii)). This Section will review these general guidelines in relation to the problems presented by the biological products under study by this Panel. It is also presented in response to the charge to this Panel to provide guidance to manufacturers for further testing required to develop acceptable evidence of effectiveness and safety.

b. *General principles*—(1) *Need.* A clinical trial is deemed necessary for a pharmaceutical or biological product when there is inadequate evidence of effectiveness and safety. The type of trial selected will be influenced by the natural history of the disease. When the natural history of the disease state is not well understood, when spontaneous fluctuations in severity are known to occur (as is the case with most allergic diseases), or when placebo effects on affected subjects are known to occur, then the trial must include appropriate comparison groups.

(2) *Purpose.* The clinical trial should be designed to determine the value of the use of a product in the recommended manner for treatment or prevention of a given disease or diseases due to a specific allergic state.

It is the view of the Panel that the products under review are to be used in the treatment or prevention of a disease or diseases and are not to be used for treatment only because of a positive skin test to a given allergen in the absence of additional clinical evidence of sensitivity to that allergen. Demonstration that a given extract is effective and safe for diagnosis of a specific allergic disease in a given individual or group of individuals does not consititute sufficient evidence with respect to effectiveness and safety for its use as a therapeutic agent; demonstration of the latter requires a separate clinical trial. A clinical trial to prove effectiveness and safety is required for each disease for which a given product will be used. For example, proof of effectiveness of ragweed pollen extract in treatment of hay fever cannot be used, by inference, to establish the value of ragweed pollen extract in asthma or atopic dermatitis. Proof of ragweed extract effectiveness in treatment of the latter two allergic disorders requires a separate evaluation for each.

On the basis of information available to the Panel, no generalization can be made about the duration of the course of administration of an allergic extract for an optimal therapeutic result. While the Panel recognizes the need for such information, it regards this as a separate and distinct question which need not be addressed in a clinical trial designed to determine the effectiveness and safety of an allergic extract.

(3) *Prerequisites.* Extensive clinical trials cannot be performed each time a new lot of a given allergenic extract is prepared. If results of clinical trials of individual lots are to be extrapolated to subsequent lots of the same product, there is an implicit assumption that the biological characteristics (in particular, potency and stability of the product) can be adequately specified and controlled by the manufacturer. This Panel has noted that this prerequisite has not yet been adequately fulfilled by many of the products under review and wishes to emphasize its importance. Further discussion of this issue can be found in the section on standardization, and specific deficiencies are noted in the reviews of individual products. Therefore, it is imperative that, before a clinical study is initiated, an acceptably standardized reference preparation be established for use in the clinical trial to allow for subsequent comparison.

(4) *Planning and coordination.* A complete detailed protocol for the conduct and analysis of the clinical trial should be prepared under the aegis of the sponsors of the study. The sponsor(s) of the study may be a manufacturer, a member of a medical faculty, a private medical practitioner, or a government agency. Results obtained from clinical trials whose protocols were not mutually agreed upon by the sponsor and the FDA prior to initiation of the study will not be excluded from consideration. However, to minimize possible conflicts in the interpretation of results, the protocol should be reviewed beforehand with the FDA and be mutually acceptable. Before initiation of a clinical trial, all protocols should be reviewed by an appropriate institutional review board on human experimentation to insure that the rights and welfare of the participants are assured, and that informed consent will be obtained.

c. *Guidelines for the conduct of a clinical trial.* (1) *Organization and personnel.* (i) Each person engaged in the conduct of or responsible for the supervision of a clinical study shall have education, training, and experience to enable that person to perfrom the assigned functions. There shall be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.

(ii) Before the initiation of the clinical study, a professional with appropriate education, training, and experience shall be identified as the principal investigator. The principal investigator shall have ultimate responsibility for implementation of the protocol and conduct of the study.

(iii) The clinical study shall be conducted in appropriate medical facilities.

(2) *Subjects.* Criteria for inclusion in the study should be stated as specifically and unequivocally as possible. Those subjects included should be representative of individuals for whom the product is to be recommended. The criteria for selection should include age, signs, symptoms, laboratory findings (e.g., diagnostic skin tests, pulmonary function tests), and other factors considered to be most characteristic of the condition whose treatment is to be studied. There should be a reasonable expectation that participants will be exposed in the usual way to the allergen that is being studied during the course of the clinical trial. Furthermore, since the severity of disease varies widely in the population, the Panel recognizes that each allergenic extract may need to be tested in groups of subjects having different degrees of diseases, from mild to moderate to severe, in order to permit extrapolation of the results of clinical trials to the total population at risk for the disease.

The Panel recognizes that the specificity of some of the disease states to be studied may be a limiting factor in clinical trials performed with the products under review. For example, the disease, asthma, represents a complex disorder in which allergy may play only a contributing role in etiology and thus the value of a single mode of treatment such as immunotherapy may be difficult to demonstrate. Failure to accurately define disease states may result in inconclusive data, even if the product under investigation is truly beneficial for a defined subtype of the disease.

The informed consent (in conformity with currently applicable governmental policy, regulation and/or law) of each participant (or legal guardian) must be obtained prior to entry into the study.

(3) *Specification of treatments.* Complete descriptions of dose, dosing interval, route of administration, duration, necessary modifications and other aspects of medical management of participants shall be clearly stated in the protocol. The dose, dosing interval, route of administration and duration of treatment used in clinical trials should approximate actual conditions of use of these products. However, only a single product or, in some cases, closely related products (e.g., short ragweed pollen extract and giant ragweed pollen extract) may be tested in a single clinical trial.

There should be both an experimental and a placebo control group in each study. The double-blind evaluation of responses remains the most reliable design. The Panel recognizes that specific circumstances may preclude the possibility of adherence to double-blind procedures. Deviation from the ideal design must be accompanied by an explanation of why rigid adherence is not feasible. Following a prearranged period, crossover of treatments may be desirable in some conditions. Information from the crossover period will be considered adjunctive to the results from the initial phase of the treatment.

(4) *Randomization.* Subjects should be assigned to test groups in such a way as to minimize bias. Allocation should assure comparibility in test and control groups of pertinent variables, e.g., age, sex, severity of disease, and the use of allergenic extracts and drugs other than the test extract. The Panel believes that an individual's degree of allergic sensitivity to a specific allergen when treatment is first initiated may be a major determinant in the response to therapy with that allergen. For certain allergic diseases (e.g., ragweed pollinosis), there is a good correlation between the severity of the disease and the degree of sensitivity to the relevant allergen as determined by one or more biologic or immunologic tests. As a consequence, the Panel recommends that the level of sensitivity of participants to the product that is being tested should be determined by a generally acceptable method or methods (e.g., end point titration skin test, leukocyte histamine release test, or RAST titer) prior to initiation of a therapeutic trial and that participants then should be allocated into groups according to their degree of sensitivity (e.g., highly allergic, moderately allergic and minimally allergic). Thereafter, participants within each of these groups should be randomly allocated to either test or control groups using a table of random numbers or other acceptable methods. Alternative entry procedures are not acceptable, nor is any method by which single codes are used for experimental and control groups.

(5) *Definitions of response.* The Panel has noted that a lack of precise, objective definitions of responses has been a limiting feature of clinical trials involving many of the products under review. The protocol should provide an unequivocal definition of an individual response, either qualitative, ranked or measurable. As there is much variation in the response to therapy of individuals, sufficiently large groups of subjects must be used so that valid comparisons can be made between test and control groups.

The responses observed must include clinical symptons and signs of disease in subjects exposed to the allergen that is being studied. The Panel recommends that, in addition, specific IgE and IgG antibodies be measured by generally acceptable methods at appropriate times during the clinical trial in order to demonstrate that the allergen that is being studied is capable of inducing expected immunologic responses such as suppression of the seasonal increase of specific IgE antibody to a seasonal allergen, and an increase in specific IgG antibody.

(6) *Collaborative investigations.* Ideally, the trial would be conducted simultaneously under the supervision of investigators in different geographic locations (since this more nearly approaches actual conditions of use of these products). When done in this fashion, the protocol should specify the design to assure maximum randomization of lots of allergenic extracts, time of entry into study, age, sex, etc., so as to prevent possible imbalances between two treatment groups.

(7) *Testing facilities operation.* (i) The clinical study will be conducted using standard methods of administering the test and control substance. These methods should be agreeable to the study director and FDA, but need not be approved by FDA beforehand.

(ii) The identity, strength, quality, and purity of each batch of a test or control substance shall have been determined before the initiation of the study. The records of these analyses shall be available to the study director. The origin and method of preparation of the test and control substances shall be documented.

(iii) The stability of each test or control substance shall have been determined before initiation of a clinical trial. Standard operating procedures shall be established and followed to ensure that the strength, quality, and purity of the test and control substances conform to specifications throughout the entire study.

(8) *Protocol.* Each study conducted for the determination of the efficacy and safety of the use of allergenic extracts for therapy shall have a written protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol shall contain, but not be limited to, the following information:

(i) A descriptive title and a clear statement of the purpose of the study.

(ii) Identification of the test and control substances by name and/or code number.

(iii) A description of the strength, quality, purity, methods of preparation, stability, storage conditions of the test

and control substances and the length of time dilutions are to be kept before discarding.

(iv) The name and qualifications of the study director and other professional persons involved.

(v) The name and address of the sponsor and the name and address of the testing facility or facilities at which the study is being conducted.

(vi) A proposed starting date and date of completion of the study.

(vii) A description of the test and control subjects who will participate in the study with the method of recruitment of potential subjects described. The criteria for identifying subjects for inclusion in the study should be stated. Only those individuals who meet the definitions of the specific condition to be treated by the use of the test substance would be included.

(viii) A description of the methods used to establish a diagnosis of the disease or condition for which the test substance is to be used.

(ix) A description of the treatment method that will be used in the study. Complete descriptions of dosage, routes of administration, sites of injection, dosage schedules, duration of tests and treatments, contingent modifications or other aspects of medical management of participants will be clearly stated in the protocol.

(x) An unequivocal definition of an individual's response to the treatment, how the reactions are to be measured and the results recorded.

(xi) A description of the statistical methods that will be used in the study.

(xii) A description of the records to be maintained.

(xiii) All changes or revisions, and reasons therefor, to an approved protocol shall be documented, signed by the study director, dated, and maintained with the protocol.

(xiv) A description of the techniques to be employed to minimize bias by both the subjects and staff.

(9) *Discovered effects.* Modified definitions, recombinations of categories, and adjustments for variables not explicitly provided for in the protocol may lead to the discovery of unanticipated effects. While the search for such additional insights is to be encouraged, they may require confirmation from additional studies before being construed to be prima-facie evidence for or against effectiveness.

(1) *Statistical analysis.* It is essential to include expert biostatistical consultation in all phases of the controlled trial, particularly during its initial design and during sample size deliberations. This would help minimize design defects which might complicate analysis. Levels of significance for all tests employed in a particular study should be defined and preferably mutually agreed upon in advance by the sponsor and FDA.

(11) *Safety during clinical studies of effectiveness.* Allergenic extracts intended for use in therapy are generally regarded as safe when used according to generally accepted methods, with due regard for the possibility of inducing an untoward allergic reaction. Nevertheless, the clinical effectiveness study may reveal unanticipated side effects and adverse clinical events. These may necessitate revision of safety standards for a specific allergenic extract. The following recommendations pertain to aspects of safety in the clinical trial.

(i) *Subjects.* There should be no unacceptable evident or anticipated levels of toxicity for participants who meet all other criteria for entry into the clinical study of effectiveness.

(ii) *Clinical observations.* Specified physical and laboratory observations shall be recorded on entry into the study and subsequently at regularly prescribed intervals. The laboratory tests selected will be those considered appropriate for the product and the condition under study.

(iii) *Adverse events.* Two classes of adverse events can be considered: those which are anticipated as concomitants or possible consequences of experimental or control treatments, and those not anticipated.

Anticipated events should be specified completely in the trial protocol, and a detailed standard form shall be developed for their recording. The relative importance of these events shall be weighed before onset of the trial preferably by mutual agreement between the sponsor and FDA. Unanticipated events may be subclassified in order of importance, e.g., sudden unexplained death, other deaths, hospitalization for illness, permanently or temporarily incapacitating events, and minor signs and symptoms. The relative importance of unanticipated events must be assessed by a comparison of their incidence in the experimental and control groups. As in the analysis of effectiveness, the degree of difference in rates which is considered to be significant should be determined beforehand.

(iv) *Continuation of trial.* Analysis of adverse events during the course of the study would permit termination of the study when and if, in the judgment of the sponsor and FDA, there was evidence of an accumulation of an excess of either anticipated or unanticipated adverse events.

(v) *Additional measures for determination of safety.* Concomitant with the authorization for general use of an allergenic extract, the Panel urges that a program for the surveillance of randomly sampled recipients be instituted and maintained for as long as the product remains on the market so that adverse effects which may occur at relatively low rates or which require many years to develop may be detected.

(12) *Final report.* A final report shall be prepared for each clinical study and shall accurately describe, but not necessarily be limited to, the following:

(i) Name and address of the facility performing the study and the dates on which the study was initiated and completed.

(ii) Objectives and procedures stated in the approved protocol, including any changes in the approved protocol.

(iii) Raw data generated while conducting the study and any transformations, calculations, or operations performed on the data.

(iv) Statistical methods employed for analyzing the data.

(v) The test and control substances identified by name and/or code number, strength, quality, and purity.

(vi) Stability of the test and control substances under the conditions of the study.

(vii) Methods used.

(viii) Description of the study subjects.

(ix) Dosage and route of administration of the test and control substances.

(x) Name of the study director and the sponsor.

(xi) A summary of the data, an analysis of the data, and a statement of the conclusions drawn from the analysis.

(xii) The location where all raw data and the final report are to be stored.

(13) *Records.* All raw data, documentation, and other information, protocols, specimens, and final reports generated during and as a result of a clinical study shall be retained. All of this material shall be made available for inspection to authorized FDA employees.

5. *Recommendations for the remaining Category IIIA Extracts for which limited clinical testing may suffice.* The bulk of allergenic extracts which have been placed in Category IIIA either lack the characteristics which make the extracts suitable for well-controlled clinical studies or have such limited or infrequent use that extensive studies are impactical. Therefore, the Panel believes that the requirements for the studies to obtain this evidence

should be modified for these remaining extracts.

There is a need for a different interpretation of the term "substantial" when applied to evidence of effectiveness for this group of products. The accumulated literature indicates that there is considerable evidence that most of the allergenic extracts of inhaled allergens in common use are effective in the diagnosis of specific inhalant allergy, but that the evidence for effectiveness in immunotherapy is not substantial. Obviously, substantial evidence for effectiveness in diagnosis is much easier to obtain than is substantial evidence for effectiveness in therapy. Thus far, any inhalant allergen which has been shown to have evidence of effectiveness in therapy has first had some evidence of effectiveness in diagnosis demonstrated. Therefore, it has been widely accepted by the allergy profession that an allergen which is useful in diagnosis of inhalant allergic diseases would by analogy be useful in immunotherapy if properly prepared and used. The Panel concurs in this belief recognizing that some allergens may be potent enough to be effective diagnostic agents but may be weak immunological stimulants when used in therapy. The basis for the logic of this assumption is that if a substance such as a pollen, animal particle, mold spore, etc. can induce the formation of antibodies by the route of natural exposure, this is prima facie evidence that the substance is an active allergen. And further, if the allergen and corresponding antibody consistently interact in a recognizable way during diagnostic procedures either on the skin, on the mucous membrane, or in vitro, then the same allergen can be used in therapy to produce a beneficial immunological effect. To date, all well-studied inhalant allergens have behaved in this manner, and nothing has appeared to contradict this assumption.

Therefore, because of the large number of products to study, it may be appropriate to place many allergenic extracts with proven diagnostic effectiveness in Category I for immunotherapy by analogy, provided there are also supplementary data for effectiveness in therapy obtained from serological studies in a limited clinical trial. The Panel would like to see the development of a simple protocol so that individual practicing allergists may participate in the clinical trials. A program in which the allergist reports patient data and the results of skin testing and sends pre- and post-treatment serum samples to a study sponsor would be very desirable. The Panel thus recommends that a more limited type of evidence of effectiveness be ultimately required for many remaining allergenic extracts not subjected to full clinical testing.

a. *Limited studies to confirm safety and effectiveness for skin test diagnosis.* The frequency of positive cutaneous and/or intradermal reactions to suitable dilutions of the allergenic extract should be shown to be significantly higher in atopic patients with a known history of symptoms to the allergen. In vitro tests such as histamine release, RAST, etc. should show significantly higher titers with leukocytes or serum from allergic versus nonallergic persons. Limited studies to confirm that allergenic extracts of suspected allergens are effective should be possible. These studies should provide the following information:

(1) *Skin testing.* (i) The extract used in the study should be adequately described with respect to source, date and method of preparation, composition, strength (dilution), etc., and lot number if a commercial preparation.

(ii) The populations used in the study should be adequately described with respect to age, sex, race, medical history, medication history and, possibly, occupation. Past history of allergic diseases in general, the sensitivity being tested in particular, and whether the subjects were symptomatic at the time of testing should be noted. The allergic population and the nonallergic control population ideally should differ only with respect to the particular allergen in question. The allergic test subjects should have an unequivocally positive, preferably strong, history of typical allergic symptoms on natural exposure to the allergen being tested. Likewise, the control subjects should have an unequivocally negative history on exposure to the same allergen.

(iii) The technique of testing should be adequately described and should include:

(*a*) How the test reagents were prepared, stored, and what precautions were used to maintain potency, e.g., preservatives and legth of time dilutions were kept before discarding.

(*b*) Volume of extract injected.

(*c*) Skin site of the tests.

(*d*) Time between injections and reading the tests.

(*e*) How the reactions were measured and the results recorded.

(*f*) Descriptions of control solutions, e.g., diluent and strength of histamine.

(*g*) Tests should be done in duplicate. For most subjects, a duplicate test should give exactly the same result. In most studies of allergens, ten-fold dilutions of the extracts are used; five or even three-fold dilutions may provide greater accuracy in determining the end point.

(*h*) The time of year and over what period of time the testing was done should be noted.

(iv) The end point titration method or a variant should be used. That is, the test should determine what concentration of allergenic extract was required to give a definite positive reaction on the allergic subjects. In the control population, the highest concentration up to and including the most concentrated solution available that gave no immediate wheal and flare reaction should also be determined. Studies in which responsiveness was measured in terms of the size of the reaction produced by a given concentration of allergen would not be considered adequate.

(v) Ideally, the tests should be read without the identity and strength of materials in the test sites being known by the observer.

(2) *In vitro tests.* The evidence of effectiveness obtained by skin testing should be augmented by the results of in vitro tests using serum or leukocytes from allergic patients. It has been shown that these tests correlate well with skin test reactivity. These tests may include histamine release from human leukocytes, radioallergosorbent tests (RAST), and quantitative radial immunodiffusion. Other tests are being developed and studied which may aid in the characterization of allergenic extracts. These include several techniques of radioimmunoassay other than RAST, such as the enzyme linked immunosorbent assay and isoelectricfocusing.

It is beyond the scope of present knowledge for the Panel to recommend standards of acceptability for each of the in vitro tests as is possible for skin testing. In general, however, for the data from in vitro testing to be acceptable as evidence of effectiveness, the materials and the method used should be adequately described, and the tests should be done in sufficient number to show reproducible results.

(b) *Limited studies to confirm safety and effectiveness for immunotherapy.* (1) Ideally, evidence of effectiveness should be based on reports containing substantial evidence obtained with scientifically sound methods as described earlier. Besides monetary and testing resource limitations, there are other constraints which preclude full clinical testing for many extracts. For example, certain allergenic extracts such as short ragweed and mountain

cedar pollen extracts have been adequately studied by employing symptom-reduction scoring techniques. There are, however, serious problems in using symptom reduction, clinical observation, or the patient's subjective evaluation as means of measuring effectiveness in immunotherapy for a large number of allergens.

(i) There is no well-defined season for many allergens, and it is difficult to monitor the degree of natural exposure. A reduction in symptoms could signify a reduction in exposure and, conversely, failure to reduce symptoms might not mean that the allergen injections failed to induce the desired immunological effect but that exposure during or following treatment was excessive.

(ii) Patients have multiple sensitivities so that while the effect of treatment is being studied with allergen A, the patient's symptoms might be influenced by concomitant exposure to allergens B, C, and D.

(iii) Symptoms similar to those used by exposure to an allergen can be caused by nonallergic irritation.

(iv) It is extremely difficult to find properly matched patient and control groups in adequate numbers for studies based on symptom reduction for a great many allergens.

(2) *Recommendations regarding limited studies.* Considering these problems and also the fact that the primary purpose for giving allergenic extract injections as a part of treatment is to induce certain beneficial immunological changes in the patient, the Panel recommends the following types of confirmatory evidence of effectiveness in immunotherapy be developed for many of the allergenic extracts in Category IIIA if controlled symptom-reduction studies are not available. Schedules for such studies should be developed by FDA for each manufacturer.

(i) Evidence of an increase in titer of specific IgG antibodies.

(ii) Evidence of a reduction in the levels of specific IgE antibodies as manifested by reduction of the skin test titer and/or a reduction of the titer of the specific IgE antibody over a period of time, measured by a suitable in vitro method.

Also the following parameters should be employed in these studies:

(iii) The extract used in the study should be adequately described with respect to source, date and method of preparation, composition, potency, dilution, etc., and the lot number if it is a commercial preparation.

(iv) The populations used in the study should be adequately described as defined above for the protocol for skin test studies, 3. a. (1)(b).

(v) The treatment procedure should be adequately described and should include:

(*a*) How the treatment materials were prepared, stored, and what precautions were used to maintain potency, e.g., preservatives and length of time dilutions were kept before discarding.

(*b*) Dosages used, both maximum single dose and total dose over the period of the study.

(*c*) Length of time during which treatments were given.

(*d*) Intervals between injections.

(vi) The serological tests to determine the antibody titers should be adequately described and performed. There should be adequate controls, and all tests should be done in duplicate.

(vii) For some extracts, it may be difficult to find a large number of patients with the specific sensitivity, but whenever possible, a sufficient number of patients should be studied to be statistically significant.

Reference

(1) King, T.P. and P.S. Norman, "Isolation Studies of Allergens from Ragweed Pollen," *Biochemistry*, 1:709–720, 1962.

III. Allergenic Extracts—Generic Statements

A. Pollen Allergenic Extracts

1. *Introduction.* Airborne pollens frequently cause pollinosis in allergic patients, which is manfested by hay fever and less often by asthma. Diagnosis is based most commonly on the following criteria:

a. Typical symptoms of hay fever or asthma following inhalation of the pollen.

b. Positive skin reaction to an appropriate dilution of allergenic extract of the pollen.

Pollinosis is produced by a specific IgE mediated reaction to the inciting pollen. Allergenic extracts of this inciting pollen are employed for both diagnosis and immunotherapy of the pollinosis.

Many pollen extracts have been shown to be effective for diagnosis of pollinosis and have been recommended to be placed in Category I for this use. Suitable studies have demonstrated that positive skin test reactions occur with high dilutions of the specific pollen extract in patients who have pollinosis from exposure to that specific pollen and negative skin test reactions occur in nonallergic controls. Eye, nose, and bronchial challenge, leukocyte histamine release, passive transfer, and radioallergosorbent tests with the extract may also be positive.

Other pollen extracts have been reported by various authors to be effective for diagnosis (Refs. 42 through 46, 48, 49, 60, 64, 66, 73 through 75, 94, 96, 99, 110, 118, 144, 151, 156, 157, and 170), but these studies were not adequately controlled. The Panel concluded that these pollen extracts should be placed in Category IIIA for use in diagnosis and believes that if properly studied, they very likely will be proven to be effective for diagnosis of pollinosis as they are analogous to the pollen extracts which already have been proven to be effective.

A few pollen extracts including short ragweed, timothy and orchard grass, and mountain cedar have been shown to be effective for immunotherapy of pollinosis caused by the homologous pollen and have been recommended to be placed in Category I for this use. Controlled studies, reviewed later in this report, have demonstrated that these pollen extracts will reduce symptoms of the appropriate pollinosis better than placebo and will induce appropriate immunological changes including: (1) rise in pollen specific IgG antibodies; (2) inhibition of the rise in pollen specific IgE antibodies which would be expected to follow natural exposure to the pollen; (3) decrease in pollen specific IgE antibodies; and (4) decrease in leukocyte histamine release by the pollen.

Many more pollen extracts have been reported by various authors to be effective for immunotherapy (Refs. 42 through 45, 48, 49, 64, 66, 73 through 75, 118, 134, 135, 144, 151, and 156), but these studies were not adequately controlled. The Panel concluded that they should be placed in Category IIIA for this use because very likely these pollen extracts ultimately will be proven to be effective for immunotherapy of pollinosis as they are analogous to the pollen extracts which already have been proven to be effective for immunotherapy.

Table I lists the generic category recommendations for the specific pollen extracts reviewed. See section IV. "Allergenic Extracts—Product Recommendations" which follows the generic statements for the Panel's recommendations regarding each manufacturers' specific pollen extracts.

TABLE.—POLLEN EXTRACT RECOMMENDATIONS

Taxonomic classification and common name	Category recommendations	
	Diagnosis	Immunotherapy
COMPOSITAE FAMILY—COMPOSITE, SUNFLOWER		
Ambrosieae—Ragweed Tribe:		
Ambrosia artemisiifolia syn. elatior—Short ragweed.	I	I.
A. trifida—Giant ragweed	I	IIIA.
A. bidentata—Southern ragweed.	IIIA	IIIA.
A. psilostachya—Western ragweed.	I	IIIA.
A. confertiflora syn. *Franseria confertiflora* or *tenuifloia*—False or slender ragweed.	IIIA	IIIA.
A. acanthicarpa syn. *Franseria acanthicarparp*—Bur ragweed.	IIIA	IIIA.
A. deltoidea syn. *F. deltoidea*—Rabbit bush.	IIIA	IIIA.
A. dumosa syn. *Franseria dumosa*—Burroweed.	IIIA	IIIA.
A. ambrosiaides syn. *Franseria Ambrosiaides*—Canyon ragweed.	IIIA	IIIA.
(Taxonomic Name not Supplied)—Woolly ragweed.	IIIA	IIIA.
Iva—Ragweed Tribe:		
Iva xanthifolia syn. *cyclachaena xanthifolia*—Burweed marsh elder.	I	IIIA.
I. annua syn. *ciliata*—Rough marsh elder.	I	IIIA.
I. frutescens—High tide bush	IIIA	IIIA.
I. microcephala	IIIA	IIIA.
I. angustifolia	IIIA	IIIA.
I. toxensis	IIIA	IIIA.
I. axillaris—Poverty weed	IIIA	IIIA.
I. acerosa	IIIA	IIIA.
I. nevadensis	IIIA	IIIA.
I. ambrosiaefolia	IIIA	IIIA.
Hymenoclea—Winged ragweed.	IIIA	IIIA.
Dicoria	IIIA	IIIA.
Xanthium—Cliocria cocklebur	IIIA	IIIA.
Anthemideae—Tansy Tribe:		
Artemisia tridentata—Common sage brush.	I	IIIA.
A. filifolia—Sand sage brush	I	IIIA.
Artemisia californica—Coastal sage brush.	I	IIIA.
A. ludoviciana—Prairie sage	I	IIIA.
A. frigida—Pasture sage	I	IIIA.
A. caudata—Tall wormwood	I	IIIA.
A. annua—Annual sage	I	IIIA.
Insect Pollinated Composites:		
Helianthease—Sunflower	IIIA	IIIA.
Solidago—Goldenrod	IIIA	IIIA.
Callistephus—Aster	IIIA	IIIA.
Chrysanthemum—Chrysanthemum.	IIIA	IIIA.
Dahlia—Dahlia	IIIA	IIIA.
Calendulus—Zinnia	IIIA	IIIA.
Cosmos—Cosmos	IIIA	IIIA.
Eupatorium—Dog fennel	IIIA	IIIA.
Taraxacum officinale—Dandelion.	IIIA	IIIA.
Helenium—Sneezeweed	IIIA	IIIA.
AMARANTHACEAE FAMILY—AMARANTH		
Amaranthus retroflexus—Common, rough, or red-root pigweed.	I	IIIA.
A. Palmeri—Carelessweed, Palmer's amaranth.	I	IIIA.
A. spinosus—Spiny amaranth	I	IIIA.
Acnida tamariscina—Western water hemp.	I	IIIA.
CHENOPODIACEAE FAMILY—CHENOPOD, GOOSEFOOT		
Salsola pestifer—Russian thistle	I	IIIA.
Kochia scoparia—Burning bush, Mexican firebush, summer cypress.	I	IIIA.
Chenopodium album—Lamb's-quarters.	I	IIIA.
Atriplex—Saltbush	IIIA	IIIA.
Beta vulgaris—Sugar beet	I	IIIA

TABLE.—POLLEN EXTRACT RECOMMENDATIONS—Continued

Taxonomic classification and common name	Category recommendations	
	Diagnosis	Immunotherapy
CANNABINACEAE FAMILY—HEMP		
Cannabis—Hemp	I	IIIA.
Humulus lupulus—Hop, common	I	IIIA.
H. Japonica—Hop, Japanese	I	IIIA.
PLANTAGINACEAE FAMILY—PLANTAIN		
Plantago lanceolata—English plantain.	I	IIIA.
P. major	IIIA	IIIA.
P. rugel	IIA	IIIA.
POLYGONACEAE FAMILY—BUCKWHEAT		
Rumex acetoselle—Sheep or red sorrel.	I	IIIA.
R. Crispus—Dock, curley	IIIA	IIIA.
R. Obtusifolius—Dock, bitter	IIIA	IIIA.
R. hymenosepalus—Canaigre	IIIA	IIIA.
GRAMINEAE FAMILY—GRASS		
Festuceae Tribe:		
Bromus mollis—Brome, soft chess.	I	IIIA.
B. inermis—Smooth brome	I	IIIA.
B. carinatus—California brome	I	IIIA.
B. secalinus—Brome chess	I	IIIA.
B. rigidus—Ripgut grass	I	IIIA.
Festuca elatior—Meadow fescue.	I	IIIA.
F. rubra—Red fescue	I	IIIA.
F. ovina—Sheep fescue	I	IIIA.
Dactylis glomerulata—Orchard, cocksfoot.	I	I.
Poa pratensis—June, meadow	I	IIIA.
P. compressa—Canada bluegrass.	I	IIIA.
P. annua—Annual bluegrass	I	IIIA.
P. trivialis—Rough bluegrass	I	IIIA.
Hordeae Tribe:		
Agropyron repens—Quackgrass, couchgrass.	I	IIIA.
A. Smithii—Western wheatgrass.	I	IIIA.
Triticum aestivum—Wheat	I	IIIA.
Hordeum jubatum—Foxtail barley.	I	IIIA.
H. murinum—Mouse barley	I	IIIA.
Lolium perenne—Perennial ryegrass.	I	IIIA.
L. multiflorum—Italian ryegrass.	I	IIIA.
L. tementulum—Darnel	I	IIIA.
Secale cereale—Rye	I	IIIA.
Aveneae Tribe:		
Holcus lanatus—Velvet, Yorkshire fog.	I	IIIA.
Avena fatua—Wild oat	I	IIIA.
A. barbata—Slender wild oat	I	IIIA.
A. sativa—Cultivated oat	I	IIIA.
Koeleria cristata—Western June grass.	I	IIIA.
Agrostideae Tribe:		
Phleum pratense—Timothy	I	I.
Agrostis alba—Redtop	I	IIIA.
Chlorideae Tribe:		
Cynodon Dactylon—Bermuda	I	IIIA.
Boutelous—Grama	IIIA	IIIA.
Phalarideae Tribe:		
Anthoxanthum oderatum—Sweet vernal.	I	IIIA.
Phalaris minor—Mediterranean canary.	I	IIIA.
P. arundinacea—Reed canary	I	IIIA.
P. canariensis—Canary	I	IIIA.
Paniceae Tribe:		
Digitaria sanguinalis—Crab	I	IIIA.
Paspalum—Dallis	I	IIIA.
Andropogoneae Tribe:		
Sorghum halepense—Johnson	I	IIIA.
S. vulgare—Sorghum	IIIA	IIIA.
Tripsaceae Tribe: *Zea Mays*—Maize, Indian corn, corn.	I	IIIA.
CYPERACEAE FAMILY—SEDGE		
Carex—Sedge	IIIA	IIIA.

TABLE.—POLLEN EXTRACT RECOMMENDATIONS—Continued

Taxonomic classification and common name	Category recommendations	
	Diagnosis	Immunotherapy
JUNCACEAE FAMILY—RUSH		
Luzula—Wood rush	IIIA	IIIA.
TYPHACEAE FAMILY—CATTAIL		
Typha latifolia—Common cattail	IIIA	IIIA.
T. angustifolia—Narrow leaf cattail	IIIA	IIIA.
CONIFERAE FAMILY—CONIFER		
Cupressinae—Junipers, Cypresses and Cedars:		
Juniperus sabinoides (*mexicana*)—Mountain cedar.	I	I.
J. virginiana—Red cedar	IIIA	IIIA.
J. bermudiana—Bermuda cedar.	IIIA	IIIA.
J. Pinchottii—Red-berried juniper.	IIIA	IIIA.
J. osteosperma—Utah juniper	IIIA	IIIA.
J. monosperma—One-seeded juniper.	IIIA	IIIA.
Chamaecyparis Lawsoniana—Port Orford cedar or cypress.	IIIA	IIIA.
Cupressus arizonica—Arizona cypress.	I	IIIA.
C. sempervirens—Italian or Mediterranean cypress.	I	IIIA.
C. lusitanica—Mexican or Portugese cypress.	I	IIIA.
C. Macrocarpe—Monterey cypress.	I	IIIA.
C. torulosa—Indian incense cedar.	I	IIIA.
Cryptomeria japonica—Japanese cedar.	I	IIIA.
Libocedrus decurrens—Incense cedar.	IIIA	IIIA.
Thuja—White cedar, arborvitae.	IIIA	IIIA.
Abietineae—Pines, spruces, and firs:		
Picus—Pine	IIIA	IIIA.
Picea—Spruce	IIIA	IIIA.
Abies—Firs	IIIA	IIIA.
Tsuga—Hemlock	IIIA	IIIA.
Taxodineae—Bald cypress and sequoias.	IIIA	IIIA.
Taxineae—Yews	IIIA	IIIA.
ARECACEAE FAMILY—PALM		
Phoenix dactylifera—Date palm	IIIA	IIIA.
Sabal—Cabbage palm	IIIA	IIIA.
CASUARINACEA FAMILY—BEEFWOOD		
Casuarina—Australian pine	I	IIIA.
SALICACEEAE FAMILY—WILLOW, POPLAR		
Salix—Willow	IIIA	IIIA.
Populus albus—White or silver	IIIA	
P. tremuloides—Poplar, aspen	I	IIIA.
P. deltoides—Poplar, cottonwood	I	IIIA.
P. nigra—Poplar, Lombardy	I	IIIA.
JUGLANDACEAE FAMILY—WALNUT, HICKORY		
Jugians californica—California black walnut.	I	IIIA.
J. nigra—Black walnut	I	IIIA.
J. cinerea—Butternut	IIIA	IIIA
J. regia—English walnut	IIIA	IIIA.
Carya pecan—Pecan	I	IIIA.
C. ovata—Shellbark hickory	I	IIIA.
C. glabra—Whitehdart hickory	I	IIIA.
C. myristiceaformis—Nutmeg hickory.	I	IIIA.
BETULACEAE FAMILY—BIRCH		
Betula—Birch	I	IIIA.
Alnus—Alder	IIIA	IIIA.
Carpinus—American hornbean, ironwood.	IIIA	IIIA.
Ostrya—Ironwood, hop-hornbeam	IIIA	IIIA.
Corylus—Hazelnut, filbert	IIIA	IIIA.

TABLE.—POLLEN EXTRACT RECOMMENDATIONS—Continued

Taxonomic classification and common name	Category recommendations	
	Diagnosis	Immunotherapy
MYRICACEAE FAMILY—BAYBERRY		
Myrica cerifera—Wax myrtle	IIIA	IIIA.
FAGACEAE FAMILY—BEECH, OAK		
Quercus—Oak	I	IIIA.
Fagus grandifolia—American beech.	IIA	IIIA.
F. sylvatica—European beech	IIIA	IIIA.
ULMACEEAE FAMILY—ELM		
Ulmus americanus—American elm		IIIA.
U. rubra—Slippery elm	I	IIIA.
U. glabra—English elm		IIIA.
U. pumila—Chinese elm	I	IIIA.
U. crassifolia—Cedar or scrub elm	I	IIIA.
U. serotina—September or red elm	I	IIIA.
U. racemosa—Cork elm	I	IIIA.
U. alata—Winged elm	I	IIIA.
Planera—Water elm	I	IIIA.
Celtis occidentalis—Hackberry	IIIA	IIIA.
C. tala—Argentine hackberry or tala.	IIIA	IIIA.
OELACEAE FAMILY—OLIVE		
Fraxinus americana—White ash	I	IIIA.
F. pennsyvanica—Red ash	I	IIIA.
F. texana—Green ash	I	IIIA.
F. velutina—Mountain ash	I	IIIA.
F. oregona—Oregon ash	I	IIIA.
Olea europaea—Olive	I	IIIA.
Ligustrum—Privet	IIIA	IIIA.
PLATANACEAE FAMILY—SYCAMORE		
Platanus occidentalis—Common native sycamore.	I	IIIA.
P. orientalis—Oriental plane tree	I	IIIA.
P. acerfolia—London plane tree	I	IIIA.
P. racemosa—Western sycamore	I	IIIA.
HAMAMELIDACEAE FAMILY—SWEET GUM		
Liquidambar styraciflua—Sweet gum.	IIIA	IIIA.
ACERACEAE FAMILY—MAPLE		
Acer saccharinum—Silver maple	I	IIIA.
A. negundo—Box elder, Manitoba maple.	I	IIIA.
A. rubrum—Red maple	I	IIIA.
A. platanoides—Norway maple	I	IIIA.
A. pseudoplatanus—Sycamore maple.	I	IIIA.
A. saccharum—Sugar maple	I	IIIA.
TILIACEAE FAMILY—LINDEN		
Tilia americana—America linden (lime, basswood).	I	IIIA.
T europese—European linden	I	IIIA.
MIMOSACEAE FAMILY—MIMOSA		
Acacia—Acacia	IIIA	IIIA.
Prosopis juliflora (syn. *glandulosa*)—mesquite, kiawe.	I	IIIA.
SIMARUBACEAE FAMILY—AILANTHUS		
Ailanthus altissima—Tree of heaven.	I	IIIA.
MORACEAE FAMILY—MULBERRY		
Broussonetia papyrifera—Paper mulberry.	I	IIIA.
Morus alba—White mulberry	I	IIIA.
Morus rubra—Red mulberry	I	IIIA.
Maclura pomifera—Osage orange	I	IIIA.
URTICACEAE FAMILY—NETTLE		
Urtica dioica (syn. *U. gracilis*)—Great nettle.	I	IIIA.
U. urens—Dwarf nettle	I	IIIA.
Parietaria officinalis—Wall pellitory	I	IIIA.

Fortunately, pollens from a relatively few species of plants commonly cause hay fever. To be important in a large number of patients, they must be windborne and simultaneously adequately buoyant, abundant, and allergenic (Refs. 42 through 44). Not all windborne pollens are sufficiently buoyant to be commonly important. Corn pollen for example, because of its great size and weight, is usually not important because it is rarely carried more than a few hundred feet from the plant. However, it is allergenic and may cause hay fever among those working intimately with the plant. Not all windborne pollens are sufficiently abundant to commonly cause symptoms. Crabgrass plants are common and their pollen is buoyant and presumably allergenic, but it is released in such small quantities that it is rarely a factor in producing pollinosis. Allergenicity is essential for a pollen to produce allergy. Pine pollen is buoyant and produced in enormous quantities but is rarely allergenic, and therefore is almost never a factor in allergic diseases. For this reason, the physician will spend most of his time working with a very small group of extracts such as those shown on Table 2 below.

However, there are times when the physician must employ extracts of pollens which rarely produce pollinosis. Therefore, for complete patient care, there must be access to properly prepared and standardized extracts of all of the very large number of pollens which may produce hay fever and/or asthma. It is for this reason that many pollen allergenic extracts have been manufactured. Manufacturers' catalogs list at least 777 pollen extracts. Because of the largeness of the list, pollen extracts were reviewed by the Panel according to the botanical family of the plant producing the pollen (Refs. 42 through 44, 64, and 151) as shown in Table 1. Certain extracts within each family were selected by the Panel as prototype extracts for more extensive review. The literature on extracts of pollens botanically related to the prototype pollen within each family was reviewed to determine whether they contain allergens similar to or different from those in the prototype extract.

The following reviews of pollen extracts are usually concerned only with effectiveness. Safety, labeling, manufacturing, and standardization of pollen extracts are covered in the general statements on these issues.

Ragweed pollen extracts are discussed more extensively.

Table 2.—List of More Commonly Used Pollen Allergenic Extracts[1]

1. Combined grasses (timothy, redtop, June, orchard, and sweetvernal grasses).
2. Bermuda grass (*Cynodon dactylon*).
3. Amaranth (pigweeds and waterhemp).
4. Salt bush (*Atriplex canescens*).
5. Burning bush (*Kochia scoparia*).
6. Russian thistle (*Salsola Pestifer*).
7. Plantain (*Plantago lanceolata*).
8. Ragweeds (*Ambrosia elatior* and *A. trifida*).
9. False ragweed (*Franseria tenuifolia*).
10. Marshelder (*Iva ciliata*).
11. Burweed marshelder (*Cyclachaena xanthifolia*).
12. Sagebush, mugwort (*Artemisia tridentata*).
13. Alder (*Alnus* spp.).
14. Birch (*Betula* spp.).
15. Ash (*Fraxinus* spp.).
16. Hickory, pecan (*Carya Pecan*).
17. Walnut (*Juglans* spp.).
18. Cedar, cypress (*Juniperus* spp).
19. Sycamore, plane tree (*Platanus* spp.).
20. Poplar, cottonwood (*Populus* spp.).
21. Oak (*Quercus* spp.).
22. Elm (*Ulmus* spp.).

[1] Adapted from Wodehouse (Ref. 43), pages 10 and 11, not listed in order of importance.

The principles discussed for short ragweed pollen extracts should apply similarly to other pollen extracts.

2. *Compositae family*—a. *Ambrosia artemisilfolia (syn. elatior) or short ragweed.* This is the prototype *Compositae* family pollen. Short ragweed is the most abundant and important ragweed in the eastern and central United States and southern Canada, and may be found from the Atlantic coast to the Rocky Mountains and on the Pacific coast (Refs. 43 through 45). Short ragweed produces abundant pollen in August and September and is usually the major cause of hay fever symptoms at this time of year in the many areas where it is abundant (Refs. 42 through 45, 64 and 151). Allergenic extracts of this pollen have been subjected to more complete study than any other extracts, and it is therefore appropriate to begin with an exhaustive consideration of short ragweed pollen allergenic extracts.

Short ragweed pollen extracts consist of mixtures of various proteins and carbohydrates. In over 10 years of studies from various laboratories, several protein constituents have been identified as putatively important allergens in ragweed by fever. This has been done by demonstrating their abilities to elicit specific wheal and flare reactions at minute concentrations in patients with ragweed pollinosis. These allergens include antigen E, antigen K, Ra3, Ra4 (BPA–R) and Ra5 (See Table 3 below) (Ref. 201).

TABLE 3.—SHORT RAGWEED

Allergens	Molecular weight	Percent of total protein	Strong skin reactivity in ragweed sensitive patients
AgE	37,800	6	Virtually all.
AgK	38,200	3	Do.
BPA–R (Ra–4)	22,800	0.9	Unknown.
Ra–3	12,100	0.4	Approximately 30 percent.
Ra–5	4,990	0.1	Approximately 7 percent to 10 percent.

It appears certain that antigen E is an extremely important allergen, but it is also clear that an individual patient may be hypersensitive to more than one antigen in the mixture, and that different individuals of a population of patients with ragweed pollinosis may be hypersensitive to different mixtures of these allergens.

Quantitatively, the above five allergens make up only approximately 10 percent by weight of the total proteins in ragweed pollen extract. Whether or not the remaining 90 percent of the protein content has any biologic function, either specific or nonspecific (e.g. adjuvant), or whether it is merely null is not known at present. Antigens K and BPA–R cross react partially with antigen E. Antigens Ra3 and Ra5 appear not to do this.

In addition, ragweed extracts contain high molecular weight carbohydrates, such as the arabinogalactan reported by Kind (Ref. 199). A polyarabinose (or arabinogalactose) is present to the extent of 40 percent of the protein by weight. Some unpublished studies by Dr. T. P. King indicate that purified carbohydrates derived from ragweed extracts do not elicit wheal and flare reactions in ragweed-sensitive patients, i.e., they are not allergenic under natural conditions of immunization. However, Kind's study indicates that purified arabinogalactan is a permeability factor when injected into mice. Its role as a permeability factor in man has not been sufficiently studied to merit even provisional conclusions. No proteolytic enzymes were detected in ragweed pollen extracts, although esterases and peptidases can be detected. The lipids associated with ragweed pollen have no known allergenic activity in ragweed, hay fever and asthma.

Thus, it is clear that ragweed pollen extracts are products of the highest complexity, containing multiple antigenic ingredients and possibly also materials with nonspecific biological properties. Accordingly, from the point of view of a rigorous assessment of potency and stability, the problem becomes a very difficult one. In addition to the complexity of the mixture of molecules in the extracts, degradation of one or more molecules in the mixture may conceivably yield inhibitory fragments or inhibitory biological activities. Also, the potency and stability of the extract as a diagnostic skin test reagent may differ from the potency and stability of the extract as a therapeutic agent. Nothwithstanding this complexity, some steps can be taken at the present time to measure potency and stability.

Most of the studies done at the Johns Hopkins University School of Medicine to demonstrate the effectiveness of short ragweed pollen extract for skin testing and immunotherapy were done with a well-standardized and characterized lyophilized extract which when reconstituted contained 27 micrograms of antigen E and 10,000 PNU/mL. (Refs. 1, 15 through 18 and 23). The Massachusetts General Hospital allergy group used a 1:50 w/v extract in their demonstration of the efficacy of ragweed pollen extract for immunotherapy (Refs. 12 through 14). Both groups tried to and often did administer the highest tolerated dose during their clinical studies.

Table 4 presents data supplied, at the request of the Panel, by manufacturers reporting their determinations of the antigen E contents of some commercially available extracts. It is evident that suitable dilutions of many of these extracts could duplicate those used in the above studies with reference to w/v, PNU content, and antigen E content.

Regarding specificity, the pollen of short ragweed cross-reacts antigenically with pollens of the other members of the *Compositae* family so that a patient sensitive to one will usually react to the other. However, antigenic differences are recognized. Short ragweed has antigens which, though somewhat related to, are clearly antigenically distinct from those of the other *Compositae:* giant ragweed (Refs. 38, 39, 41, 43, 44, 47, 48, 91, 158, and 163); southern ragweed (Refs. 41 and 158); western ragweed (Refs. 41, 43, 44, 46, 48, 91, and 158); Franseria (Refs. 41, 43 through 46, 91 and 158); Iva (Refs. 41, 43, 44, 48, 49 and 158); *Xanthium* (Refs. 41, 43 through 45 and 158); *Antemisia* (Refs. 41, 43 through 46, 158 and 162) and insect pollinated *Compositae* (Refs. 43 through 45, 47, 50, 51, 94, 163 and 164). These cross-reactions and antigenic differences will be discussed in more detail as each *Compositae* family member is reviewed in the ensuing sections.

TABLE 4.—Antigen E Contents of Some Lots of Commercially Available Extracts of Short Ragweed Pollen Reported by Manufacturers

Company	w/v	PNU/mL	Antigen E microgram/mL
Allergy Laboratories of Ohio.	1:10	No data	52, 233, 239, 544
Antigen Laboratories	1:20	do	170
Center Laboratories	No data	78,000	300
		20,000	75
Greer Laboratories	1:10	48,000	187–407
		88,000	
Hollister-Stier Laboratories.	1:10	No data	184–400
	1:20	do	175–340
Iatric Corporation	1:20	do	420–500

Criteria for effectiveness of ragweed pollen extracts for skin test diagnosis. The following points were considered in evaluating studies of ragweed pollen extract effectiveness for use in diagnosis and were similarly considered for other pollen extracts where the criteria apply.

(1) *Correct clinical diagnosis.* The studies should demonstrate that typical symptoms of hay fever and/or asthma follow ragweed pollen exposure and that the patient, therefore, was clinically sensitive to ragweed pollen. Studies which correlate symptoms with the seasonal rises and falls of the pollen count are a good way to confirm this (Refs. 15 and 23). Patients with negative skin tests to ragweed pollen very rarely, if ever, have a firmly established clinical diagnosis of ragweed pollinosis (Ref. 1). Symptoms in the ragweed pollen season may be caused by other concomitantly acting allergens to which the patient is sensitive, such as house dust, mold, or animal dander (Ref. 1). The diagnostic specificity of skin test reactions to ragweed pollen extract should be studied in patients without symptoms to concomitantly acting allergens (Ref. 1).

(2) *Patient variability.* Clinically sensitive patients fulfilling the first criteria usually have positive skin tests to ragweed pollen extracts, but do not have equal skin reactivity. Most sensitive patients will react to very low doses of ragweed pollen extract; a few will react to high doses only; and possibly a very few will not react at all, even with high doses (Refs. 1, 2, 4, 7, and 8). This is demonstrated by use of skin test end-point titrations employing constant volumes and variable dilutions.

(3) *Reaction specificity.* Irritative reactions must be differentiated from specific reactions. The diagnostic wheal

and flare must be shown to be induced by ragweed pollen antigen and not be some other irritative substance in the extract, diluent, syringe, or needle (Ref. 1). Appropriate control skin tests performed on nonallergic patients with the extract and on the tested patient with diluent, syringe, and needles are essential. Disposable syringes and needles are useful because they are almost invariably free from contamination by irritants or irrelevant antigens at the time of first use. The injection technique must be sufficiently gentle to avoid the normal triple response to skin injury (Ref. 9). Dermatographism and universal reactors must be ruled out.

(4) *Clinically insensitive patients.* Patients who do not have hay fever, asthma, or other symptoms upon exposure to ragweed pollen may nevertheless have skin reactivity to ragweed pollen extract. Many atopic patients clinically free of symptoms from ragweed pollen but with asthma and/or hay fever symptoms induced by exposure to allergens other than ragweed pollen (clinically insensitive patients) will have a positive skin test to ragweed pollen extract (Refs. 1 and 4 through 8). This type of clinically insensitive patient is usually "less skin reactive" than the clinically sensitive patient in that higher doses on the average are found to be needed to elicit the skin reaction when end-point titration methods are used. Nevertheless, there are some clinically insensitive patients who react to low doses of extract and some clinically sensitive patients who react only to high doses so that there is overlap and, therefore, a skin test reaction to ragweed pollen extract by itself is not diagnostic of clinical allergy to ragweed pollen (Refs. 1 and 4 through 8).

(5) *Extract potency.* Misleading negative or low-titer skin reactions in clinically allergic patients may be due to extracts of reduced potency (Refs. 1 and 3). Some commercial extracts may be relatively impotent at the time of purchase by the physician (Ref. 3). The skin reacting allergens, particularly the most important one, Antigen E, may be lost through deterioration in storage, particularly in the very dilute solutions used for critical end-point titration unless stabilizers and other protective measures are employed (Ref. 1).

Critique of short ragweed pollen studies on effectiveness for skin test diagnosis. The Panel reviewed a number of studies which individually or collectively indicate that a properly performed and interpreted skin test may be of considerable value as a diagnostic aid (Refs. 1 through 8). The presence of both skin reaction to ragweed pollen extract and hay fever and/or asthma after ragweed pollen exposure is usually diagnostic of ragweed pollinosis. Both phenomena are necessary to have reasonable certainty of the diagnosis. The more typical the symptoms of pollinosis are (erythema, itching and tearing of the eye, repetitive sneezing and palatal itching), the closer the relation of these symptoms is to ragweed pollen exposure, the smaller the amount of ragweed pollen needed to elicit skin reactivity, and the smaller the number of factors other than ragweed pollen which produce hay fever and/or asthma, then the greater the reliability of the diagnosis that allergy to ragweed pollen is at least one cause of the patient's hay fever and/or asthma (Refs. 1 through 8). Therefore, properly prepared and used short ragweed pollen extract is considered to be an effective aid for the diagnosis of ragweed pollen-induced hay fever and/or asthma. These studies are reviewed in detail in the paragraphs which follow.

Norman, Lichtenstein, and Ishizaka (Ref. 1) studied 18 hay fever patients who had an increase in symptoms of hay fever as manifested by a correlation of symptom scores with pollen counts during the ragweed hay fever season. Skin tests with ragweed pollen extract revealed that 16 reacted to 1 PNU/mL or less, 1 reacted to 10 PNU/mL, and 1 did not react to 1,000 PNU/mL. They also studied 19 hay fever patients who did not show a correlation of symptom scores with pollen counts during the regweed pollen season and found that skin tests with the same ragweed pollen extract revealed that 7 reacted to 1 PNU/mL or less, 5 reacted to 10 PNU/mL, 1 reacted to 100 PNU/mL, and 6 did not react to 1,000 PNU/mL. Skin tests were done with disposable syringes by the intradermal method using a constant injection volume of 0.05 mL and end-point titration. Whole short ragweed pollen extract was prepared by Hollister-Stier Laboratories as a lyophilized extract containing 27 micrograms (mcg) antigen E per 10,000 PNU. Significant correlations were shown between dose of pollen as measured by ragweed pollen counts, severity of symptoms as measured by magnitude of symptom scores, intensity of skin sensitivity as measured by end-point titration, level of IgE antibody to ragweed pollen as measured by RAST, and cell sensitivity to ragweed pollen extract as measured by leukocyte histamine release. This paper shows that allergic patients with typical symptoms of hay fever in the ragweed season usually have positive skin reactions to low concentrations (1 PNU/mL or less) of ragweed pollen extract. Allergic patients who do not have symptoms of hay fever after exposure to ragweed pollen may have positive skin tests to ragweed pollen extract even in low concentrations, but tend to require higher concentrations of ragweed pollen extract to produce skin reactions than do those with ragweed symptoms.

Bruce, Rosenthal, Lichtenstein, and Norman (Ref. 2) studied 36 patients with ragweed pollen asthma (usually also associated with hay fever) who had positive skin tests to ragweed pollen extract in a dilution of 50 PNU/mL or less. All had positive bronchial challenge tests, and 30 of 33 had leukocyte histamine release produced by this ragweed pollen extract. Four control patients with a history of seasonal asthma corresponding to the ragweed season had negative bronchial challenge tests and either negative skin tests to ragweed pollen extract (3 patients) or positive reaction to 100 PNU/mL (1 patient). Skin tests were done in the same manner described above. Short ragweed pollen extract was prepared by Center Laboratories as a lyophilized extract assayed to contain 26 to 67 micrograms antigen E per mL and 10,000 PNU per mL. This study shows an excellent correlation between the results of skin, bronchial challenge, and leukocyte histamine-release tests and was interpreted by the authors as suggesting that "the response of lung and skin mast cells and circulating basophils to ragweed antigens occur as if they were a single population of cells in equilibrium with the pool of IgE anti-ragweed antibody."

Gleich, Larson, Jones and Baer (Ref. 3) studied seven patients with ragweed pollen hay fever. All had positive skin reactions to ragweed pollen extracts. There was correlation between the potency of the extract as determined by the intradermal skin test end-point titration and its potency as determined by both antigen E content, and RAST inhibition. Eleven different extracts were tested which were purchased from 11 different manufacturers. "It was remarkable that even though these extracts were close to the same potency in terms of the manufacturer's estimate (either w/v or PNU) nonetheless their potency by skin test titration varied by almost 1,000-fold." This paper emphasizes the importance of potent extracts for effective skin test diagnosis.

Lindblad and Farr (Ref. 4) studied 66 patients with a well-documented history of rhinitis and/or asthma during the ragweed pollen season. Fifty-six (85

percent) gave a positive skin reaction to ragweed pollen extract containing 0.001 mg N per mL. On the other hand, of 100 patients who had "a completely negative history of nasal or respiratory symptoms which could in any way be interpreted as being on an allergic basis," none had a positive skin test to ragweed extract containing 0.001 mg N per mL, and only 8 reacted to ragweed pollen extract containing 0.01 mg N per mL. Skin tests were done by the intradermal method using disposable syringes. Extracts were made by the Allergy Laboratory, Montefiore Hospital, Pittsburgh, PA, by extracting dry defatted pollen with Coca's solution for 24 to 48 hours. This paper emphasizes the important fact that very few patients with no evidence of respiratory allergic symptoms react to skin test with small amounts of ragweed pollen extract; whereas most patients with bona fide ragweed hay fever and asthma do react. However, there are a small number of exceptions.

Curran and Goldman (Ref. 5) studied 100 individuals who had "no personal or family history of allergy." Skin tests were done by the scratch method using 1:10 dilution of ragweed pollen extract; and by the intradermal method using 1:1,000 dilution of the extract if the scratch test was not clearly negative. Ragweed extracts were obtained from Center Laboratories, and the Panel presumed that the concentrations referred to were w/v concentrations. Three of the 100 patients reacted to the ragweed pollen extract scratch test, and 2 of the 97 patients who did not react to the scratch test reacted to the intradermal test. In contrast, individuals with a definite seasonal history of rhinitis or asthma usually responded with a positive skin test to these extracts applied in this manner. This paper is important because it shows that nonallergic patients without family or past history of allergic disease usually have negative scratch test reactions to ragweed pollen extract 1:10 w/v and negative intradermal reactions to 1:1,000 w/v. However, 5 percent of these nonallergic individuals do show positive reactions.

Fontana, Wittig, and Holt (Ref. 6) studied 100 children with a variety of minor complaints, none of them suggestive of allergy. Only one of these patients reacted to an intradermal test with ragweed pollen extract of 500 PNU/mL. On the other hand, of 100 allergic children with asthma or hay fever without regard to increase in symptoms in the ragweed season, 56 reacted to ragweed pollen extract given in this manner. This study shows that only 1 percent of nonallergic children react to an intradermal test with 500 PNU/mL of ragweed pollen extract. The data with regard to allergic children are difficult to interpret because the authors do not distinguish allergic children with symptoms due to exposure to ragweed pollen from those without symptoms upon exposure to ragweed pollen. This extract was made by M.B. Strauss in the Allergy Laboratory at University Hospital, New York City, by extracting defatted pollen in phosphate-buffered saline.

Connell and Sherman (Ref. 7) studied the relationship between intracutaneous skin test, as determined by end-point titration, and the skin sensitizing antibody titer in 212 randomly selected patients. In general, there was an inverse correlation between the titer of skin sensitizing antibody and the end point of the intracutaneous test, so that patients with a high titer of skin-sensitizing antibody to ragweed had skin reactions to very low concentrations of ragweed pollen extract, and those with low concentrations of antibody had skin reactions only to high concentrations of ragweed pollen extract. The source of the extracts was not stated.

Connell and Sherman (Ref. 8) studied 61 patients with typical symptoms of hay fever during the ragweed pollen season. All had positive interadermal skin reaction to low dilutions of ragweed pollen extract (1 PNU/mL or less), and high titers of skin sensitizing antibody. On the other hand, 40 patients, who were asymptomatic in the ragweed season but who gave positive reaction to intradermal tests with 100 or 1,000 PNU/mL, had low titers of skin sensitizing antibody or none that could be detected. This study indicates that allergic subjects who deny symptoms of hay fever or asthma in the ragweed season may have positive intradermal skin tests to ragweed pollen extract. In this event, the titer of skin-sensitizing antibody is nil or low and in general distinctly lower than that in ragweed-sensitive patients. Moreover, positive skin tests in asymptomatic patients require high concentrations under most circumstances (100 or 1,000 PNU/mL), while those in symptomatic patients are usually to low concentrations (1 PNU/mL or less). The source of the extracts was not stated.

Criteria for effectiveness of ragweed pollen extracts for immunotherapy. Proper evaluation of studies on the effectiveness of these products includes consideration of the following:

(1) *The need for correct diagnosis.* It is essential to study patients who have unequivocal manifestations of hay fever and/or asthma reproducibly induced by ragweed pollen and a positive skin test induced by low (10 PNU/mL or less) concentrations of ragweed pollen extract.

(2) *The need for reliable patients.* Patients must be capable of keeping medical appointments, and of taking medication as prescribed. They must be able to record symptoms and medication in appropriate diaries which are used for calculating symptom-medication scores and which are the only reliable basis known to date for quantitating severity of hay fever symptoms.

(3) *The need for a clearly defined exposure to ragweed allergen.* The ragweed season is easily defined in a given area by performing pollen counts. In some geographical areas, ragweed pollen is the principal airborne allergen during its pollinating season, permitting the study of patients for whom investigators can be relatively sure that ragweed pollen is the cause of the symptoms under treatment. In this regard, ragweed pollen is a better subject for immunotherapy studies than allergens such as oak pollen or house dust which are prevalent at times when many other airborne allergens are present, making it difficult to be sure that they are the cause of the symptoms under observation. This feature has much to do with the fact that most satisfactory studies of the effectiveness of allergen immunotherapy have been done with ragweed pollen extracts.

Comparison of symptoms and signs of hay fever and/or asthma before, during, and after the ragweed pollen season with relation to the magnitude of the ragweed pollen count permits a relation to be established between the amount of ragweed pollen exposure and the severity of the disease, and therefore affords a basis for determining the effectiveness of immunotherapy with ragweed pollen extract in relation to a known dose of ragweed pollen (Refs. 15, 17, 18, and 23).

(4) *The need for objective and quantitative evidence of manifestations of hay fever and asthma.* A means, such as the daily symptom diary, must be used to quantitatively assess the severity of the symptons and signs of hay fever and asthma.

(5) *The need for study of immunologic phenomena which might relate to effectiveness and specificity.* It is possible to study in treated and control patients skin and leukocyte reactivity to ragweed pollen extracts, blocking antibody or IgG anti-ragweed antibody levels, and specific IgE anti-ragweed antibody levels.

(6) *The need for controls*—(i) *For therapeutic measures other than immunotherapy.* Matched groups of equal size, treated with the same drugs or other measures, should be employed, one group receiving specific immunotherapy and the other not.

(ii) *For variations in host factors.* Before the onset of the study, the patients should be matched as closely as possible in pairs with reference to severity of disease, duration of disease, age, sex, and race. One member of each pair should be assigned to each treatment group.

(iii) *For previous immunotherapy.* Patients preferably should have had no immunotherapy before the onset of the study. If patients have previously had fairly equal amounts of immunotherapy, they can be paired as described in paragraph (ii) above and assigned in random fashion to two treatment groups, one to continue specific immunotherapy, the other to cease specific immunotherapy (Ref. 12).

(iv) *For physicians and patient bias.* The study must be truly double-blind; neither physician nor patient should know whether or not any particular patient is receiving immunotherapy. This design requires an adequate placebo injection for the patients in the group receiving no immunotherapy. This placebo should have similar color and produce skin reactions and, therefore, ideally should contain some non-specific coloring matter and histamine (Ref. 14) or coloring matter and allergens other than ragweed to which the patient is sensitive (Refs. 12 and 13).

(7) *The difficulties in conducting studies*—(i) *Ethical restraints.* Controlled studies of immunotherapy for ragweed pollinosis began at a time when there was general agreement among allergists that such immunotherapy relieved manifestations of hay fever and asthma induced by ragweed pollen. Patients with ragweed hay fever were used for the controlled studies because it was felt that manifestations of hay fever occurring in the placebo-treated group could be relieved with oral medication; patients with asthma were excluded for fear of having harm from asthma come to members of the placebo-treated group. Probably, for this reason, there are to date only two controlled studies of immunotherapy for ragweed pollen asthma (Refs. 19 and 200).

(ii) *The variable course of the disease.* The natural history of ragweed pollen-induced hay fever and asthma in any given patient is most variable. Remissions can occur that are apparently spontaneous and unrelated to the operation of any known factor. Remissions may also occur after eliminating or favorably modifying many known adverse factors including specific antigen exposure (both ragweed pollen and other concomitantly reacting antigens such as house dust, molds, and animal danders), respiratory tract irritant exposure (such as tobacco smoke), and anxiety. Drug therapy will and should be used, and it will help to a greater or lesser degree depending on the response of the patient, the selection of the drug, and whether the drug used customarily exerts a strong favorable effect (as with certain corticosteroids) or a less strong but still favorable effect. Exacerbations may occur spontaneously or following increasing action of any, some, or all of the adverse factors listed above.

(iii) *The use of multiple therapeutic measures simultaneously.* Proper treatment of the ragweed allergic patient consists of favorably modifiying all demonstrated adverse factors and using appropriate drugs. Therefore, multiple therapeutic measures are usually employed together with the extracts. The increased motivation of the patient that occurs when he follows such a program should also exert a favorable effect, the so-called "Hawthorne Effect" (Ref. 21). Under these circumstances, the ability of both patient and physician is limited with reference to determining the specific favorable effect of any particular measure.

Critique of short ragweed pollen extract studies on effectiveness for immunotherapy. This subject is very well covered in four reviews (Refs. 10 through 12 and 197). The evidence may be summarized as follows:

(1) Sufficient immunotherapy with ragweed pollen extract will reduce the severity of symptoms of ragweed pollen hay fever and probably asthma. Johnstone (Table 5) showed that therapy with regweed pollen extract was more effective than placebo for eliminating symptoms of asthma in the ragweed pollen season (Ref. 19). He also presented evidence suggesting that ragweed pollen extract was more effective than placebo for reducing the severity of hay fever symptoms in the ragweed pollen season, but did not confirm this because a satisfactory method for quantitating severity of hay

fever symptoms was not used. Lowell and Franklin's studies at the Massachusetts General Hospital (Table 6) and the Johns Hopkins Hospital studies (Table 7) clearly established that ragweed pollen extract was more effective than placebo for reducing the severity of hay fever symptons in the ragweed pollen season (Refs. 12 through 18 and 23).

(2) The effect of ragweed pollen extract is specific. Lowell and Franklin (Table 6 below) showed that ragweed pollen extract was more effective than allergenic extracts other than ragweed (including tree, grass, and plantain pollen extracts) for reducing the severity of hay fever symptoms in the ragweed pollen season (Refs. 12 through 14).

(3) The effect is dose related. Johnstone (Table 5 below) showed that ragweed pollen extract 1:200 w/v was significantly more effective than the same extract diluted to 1:10,000,000 w/v or a placebo, and was slightly more effective than the 1:5,000 w/v dilution of the same ragweed pollen extract for eliminating symptoms of asthma in the ragweed pollen season. Franklin and Lowell (Table 6 below) demonstrated that 0.1 to 0.5 (median 0.3) mL of ragweed pollen extract 1:50 w/v was more effective than 0.1 to 0.4 (median 0.3) mL of ragweed pollen extract 1:1,000 w/v for reducing the severity of hay fever symptoms in the ragweed pollen season. The Johns Hopkins Hospital studies (Table 7 below) showed that an average cumulative perseasonal dose of 32 micrograms of ragweed pollen antigen E, or 829 PNU of ragweed pollen extract was no more effective than placebo in relieving symptoms of hay fever in the ragweed pollen season, whereas average preseasonal cumulative does of 252–1,000 micrograms of ragweed pollen antigen E, or 2,442 to 21,200 PNU of ragweed pollen extract were significantly more effective than placebo for relieving such symptoms. All of these studies reported that dosage of ragweed pollen extract must be cautiously increased in order to avoid or minimize local and constitutional reactions. An optimal dose could be obtained in most circumstances which produced reduction in severity of pollinosis symptoms with acceptable local reactions and without systemic reactions.

TABLE 5.—RESULTS OF PERENNIAL TREATMENT WITH RAGWEED POLLEN EXTRACT (REF. 19)

Diagnosis			Treatment dose	Results of treatment							
				Hay fever			Asthma				
Total Number of patients	Hay fever plus asthma number of patients	Hay fever alone number of patients		Same	Worse	Better	Lost [1]		Appeared [2]		Significant effect on eliminating asthma
							Number	Percent	Number	Percent	
26	14	12	Placebo	13	7	6	1	7	5	42	No.
31	21	10	1:10,000,000 "Hansel dosage"	16	7	8	4	19	6	60	No.
26	15	11	1:5,000 "Ratner dosage"	16	1	9	9	60	0	0	Yes, P<0.01.
29	22	7	1:200 "Highest tolerated dose"	14	1	14	15	68	0	0	Yes, P<0.001.

[1] Lost means pollen asthma was present before treatment and lost during treatment.
[2] Appeared means pollen asthma was absent before treatment and apprared during treatment.

TABLE 6.—MASSACHUSETTS GENERAL HOSPITAL HAY FEVER IMMUNOTHERAPY STUDIES

Reference	Year	Number of patients	Dose (perennial method)	Average symptom scores	Treatment B more effective than treatment A
14	1960	25	A. Placebo	[1] 15.37	Yes.
		22	B. WRE [4] to tolerance usually 75,000 noon units every 2 to 4 weeks	[1] 7.16	P<0.05.
15	1961	12	A. Placebo	[1] 11.49	Possibly.
		15	B. WRE [4] to tolerance usually 75,000 noon units every 2 to 4 weeks	[1] 6.11	
12	1963	12	A. Placebo	[2] 13.50	Yes.
		12	B. WRE [4] to tolerance dose presumably similar to that used in 1961 and 1962	[2] 9.05	P<0.05.
13	1964	12	A. WRE [4] 1:1000 w/v 0.01 to 0.4 ml. median 0.3 ml	[3] 4.476	Yes.
		12	B. WRE [4] 1:150 w/v 0.1 to 0.5 ml. median 0.3 ml	[3] 2.054	P<0.05.

[1] Sum of "refined scores" for 2 weeks ending Sept. 7.
[2] Sum of total scores Sept. 2 to Sept. 30.
[3] Sum of symptom scores Aug. 13 to Sept. 3.
[4] WRE = whole ragweed extract.

TABLE 7.—JOHN HOPKINS HOSPITAL RAGWEED HAY FEVER IMMUNOTHERAPY STUDIES

Reference	Year	Number of patients	Method	Average cumulative yearly dose	Average symptom index [1,2]	Ragweed immunotherapy more effective than placebo
15	1963	20	Preseasonal	Placebo	9.4 [1]	
		20		AgE [3] 3.7 mcg	[1] 11.1	No.
15	1964	19	Preseasonal	Placebo	[1] 9.6	No.
		18		AgE 32 mcg	[1] 8.3	No.
		19		WRE [4] 829 PNU	[1] 7.7	No.
15	1965	27	Preseasonal	Placebo	[1] 8.0	
		29		AgE 252 mcg	[1] 6.8	Yes.
		20		WRE 2,442 PNU	[1] 5.8	Yes.
15	1966	23	Preseasonal	Placebo	[1] 6.8	
		27		AgE 743 mcg	[1] 5.1	Yes.
		16		WRE 9,483 PNU	[1] 4.2	Yes.
23	1967	20	Perennial	Placebo	[1] 8	
		19		AgE 1,400 mcg	[1] 4.8	Yes.
		13		WRE 16,000 PNU	[1] 4.1	Yes.
23	1968	16	Perennial	Placebo	[1] 8	
		19		AgE 1,900 mcg	[1] 5.8	Yes.
		10		WRE 24,000 PNU	[1] 3.2	Yes.
17	1968	21	Preseasonal	Placebo	[1] 11.2	
		18		AgE 1,000 mcg	[1] 7.9	Yes.
		19		WRE 24,000 PNU	[1] 8.0	Yes.
		20		AgE and AgK	[1] 6.4	Yes.
18	1969	21	Preseasonal	Placebo	[1] 8.4	
		17		WRE 21,260 PNU	[1] 4.3	Yes.
		33		Alum PPT 23,501 PNU WRE [6]	4.2	Yes.
16	1967	17	Perennial	WRE <1 PNU	[2] 42	
		18		WRE 22,000 PNU	[2] 22	Yes.
27	1970	20	Preseasonal	Placebo	[1] 8.7	
28		20	Preseasonal	Alum PPT WRE 13,746 PNU	[1] 6.4	Yes.
		26	Perennial	Alum PPT	[1] 5.0	Yes.

[1,2] Symptom index calculated in different units in [1] and [2].
[3] AgE = ragweed antigen E.
[4] WRE = whole ragweed extract.
[5] AgK = ragweed antigen K.
[6] Alum PPT WRE = alum precipitated whole ragweed extract.

(4) The effect is associated with specific immunologic responses. There is considerable evidence of specific immunologic responses to ragweed pollen extract used for immunotherapy of ragweed pollen induced hay fever and asthma. These responses may be classified as follows:

(a) An induction of specific 1gG anti-ragweed antibodies (Refs. 7, 15 through 18, 23 through 26, 29, 31, and 34 through 36). These so-called "blocking antibodies" appear regularly after sufficient immunotherapy and may be readily demonstrated by their ability to bind ragweed pollen antigen either in readioimmunoassays or in bioassays utilizing skin test or histamine release techniques;

(b) A reduction in specific IgE anti-ragweed antibody rise during and immediately after the ragweed pollen season (Refs. 25 through 28, and 37). In the placebo treated patient, there is a regular rise in specific IgE anti-ragweed antibody which starts in the ragweed pollen season, reaches a high in the months immediately thereafter and slowly falls to a low in the period just before ragweed pollination. A patient given a sufficient amount of ragweed pollen extract will often show a rise in specific IgE anti-ragweed antibody in the first months of immunotherapy with a subsequent fall and no rise in the ragweed pollen season;

(c) A progressive reduction in circulating IgE anti-ragweed antibody levels during many years of immunotherapy (Refs. 7 and 33);

(d) A progressive decrease in skin test reactivity to ragweed pollen extract many years of immunotherapy (Refs. 7 and 30) and

(e) A decrease in leukocyte sensitivity to release histamine after exposure to ragweed pollen extract in vitro (Refs. 16 through 18, 26, and 34 through 36).

There is an appropriate correlation between reduction in severity of ragweed pollinosis symptoms and each of the five immunologic phenomena listed above, but none of the phenomena are uniformly correlated with reduction in severity of symptoms, and no single one can be used as a direct idicator of therapeutic effectiveness.

(5) Immunotherapy was not effective according to one study (ref. 20). This is the only controlled study found in which the uthors conclude that immunotherapy with ragweed pollen extract does not benefit patients with ragweed pollen hay fever. However, this study does not fulfill the criteria of an adequate and well controlled clinical trial because it failed to quantitate severity of hay fever symptoms either in the initial pairing of patients for ragweed and placebo treatment groups or in the evaluation of results. Both the treatment group receiving ragweed pollen extract and the group receiving placebo had similar numbers of days with hay fever symptoms in the ragweed pollen season. This finding is not surprising because the other studies (Refs. 12 through 18 and 23), all of which were designed to quantitate the severity of hay fever symptoms, demonstrated a greater reduction in the severity of symptoms of ragweed hey fever rather than showing a decrease in total days with hay fever symptoms in the ragweed pollen extract treated groups than in the placebo treated groups.

Therefore, the Panel concluded that properly administered immunotherapy with short ragweed pollen extract is an effective method for reducing the severity of symptoms from ragweed pollen hay fever and/or asthma in many patients.

Recommendations. The Panel recommends that short ragweed pollen extract be placed in Category I for both skin test diagnosis and for immunotherapy of ragweed pollen hay fever and asthma.

b. *Giant ragweed. Ambrosia trifida* (giant ragweed) occurs in most places where ther is short ragweed, but is usually less abundant. In certain areas in the middle West, it may produce a greater share of airborne pollen than short ragweed. The pollen is an important cause of hay fever and

asthma (Refs. 42 through 45, 64, 66, and 151).

Very little work has been done to determine the antigenic constituents of giant ragweed. Trifidin A, a relatively pure protein material, was isolated from giant ragweed extracts by Goldfarb et al. in 1958 (Ref. 198), and it gave skin reactions in patients with ragweed hay fever. Little is known of other important allergens in giant ragweed.

There is considerable evidence indicating that extracts of giant and short ragweed pollen contain both similar and distinct allergens. Cooke and Vander Veer (Ref. 107) in a series of 26 cases and Vander Veer, Cooke and Spain (Ref. 156) in a series of 800 cases showed that those who reacted positively with direct skin tests to one of these antigens almost invariably reacted similarly to the extract of the other pollen. This work has been repeatedly confirmed by others (Ref. 38). On the other hand, differences in skin sensitivity to extracts of giant and short ragweed pollens can be shown when subjects are tested with very low concentrations (Refs. 38 and 39), and constitutional and local reactions may occur when patients who tolerated a given immunotherapy dose of giant ragweed pollen extract are transferred to presumably equivalent doses of short ragweed pollen extract (Refs. 38 and 39). There are also reports of occasional patients who have symptoms of hay fever after exposure to short but not after exposure to giant ragweed pollen and vice versa (Ref. 39). From this type of evidence has come the common practice of using a mixture containing both giant and short ragweed pollen extracts for skin testing and immunotherapy (Refs. 40 and 47).

Wodehouse (Ref. 46), Simon (Ref. 163) and Prince and Secrest (Ref. 48) using passive transfer neutralization techniques, Wodehouse (Ref. 47) using gel diffusion techniques, Yunginger and Gleich (Ref. 41) using radioimmunoassay techniques, and Leiferman, Gleich, and Jones (Ref. 158) and Bernstein et al. (Ref. 91) using radioallergosorbent techniques have demonstrated both cross-reactivity and antigenic differences between giant ragweed and short ragweed (Refs. 41, 47, 48, 91, 158, and 163), southern ragweed (Refs. 41 and 158), western ragweed (Refs. 41, 48, 91, and 158), *Franseria* (Refs. 41, 91, and 158), *Iva* (Refs. 41, 48, and 158), *Xanthium* (Refs. 41 and 158), *Artemisia* (Refs. 41, 46, and 158), goldenrod (Ref. 163), cosmos (Ref. 163), dandelion (Ref. 163), and sunflower (Ref. 163).

Effectiveness of giant ragweed pollen extracts. (1) *Skin test diagnosis.* The studies discussed above indicate that extracts of giant and short ragweed or equal parts mixtures of both extracts can be used interchangeably for skin test diagnosis of hay fever and/or asthma due to the inhalation of ragweed pollen in many patients, but that both extracts should be available for use in skin testing the occasional patient who is mainly sensitive to only one of these two species of ragweed.

(2) *Immunotherapy.* Short rather than giant, ragweed pollen extract has been used for those controlled studies of immunotherapy in which the type of ragweed pollen used in the extract was clearly stated (Refs. 15 through 18 and 23). This situation pertains because these studies concerned antigen E and were done with a single batch of short ragweed pollen extract. These studies demonstrate the effectiveness of short ragweed pollen extract (and antigen E) for reducing the severity of symptoms of hay fever from inhaling ragweed pollen. No similar controlled studies have been done with giant ragweed pollen extract and there is, therefore, no conclusive demonstration of the effectiveness of giant ragweed pollen immunotherapy for reducing the severity of symptoms of hay fever and/or asthma from inhaling ragweed pollen. As noted earlier, uncontrolled studies suggest, but do not prove, that immunotherapy with the type of ragweed pollen (giant or short) to which the patient is most sensitive may sometimes be essential for relief of symptoms (Ref. 39).

Recommendations. The reported results of skin testing with giant ragweed pollen extracts in allergic and nonallergic patients indicate that these extracts are effective for skin test diagnosis. The Panel found only circumstantial evidence indicating that these extracts are effective for immunotherapy, but recommends that they should be available for immunotherapy of patients allergic to the distinctive antigens of giant ragweed pollen which differ from those in short ragweed pollen. The Panel recommends that giant ragweed pollen extract be placed in Category I for skin test diagnosis and Category IIIA for Immunotherapy.

c. *Southern ragweed pollen extracts. Ambrosia bidentata* or southern ragweed is locally abundant in the Ozark region and is found between southern Illinois and Louisiana, and in Missouri, Arkansas, Nebraska, Kansas, Oklahoma, and Texas. It may gow as a weed in heavily pastured areas where it may account for 90 percent of the summer plant cover. It undoubtedly contributes greatly to the atmospheric pollen load within its restricted range and may be a cause of hay fever and asthma (Refs. 42 through 45, 64, and 151). It is generally stated that the pollen of southern ragweed cross-reacts with that of short ragweed, so that a patient sensitive to one will usually react to the other (Refs. 43 and 44). However, antigenic differences are recognized, and southern ragweed pollen clearly has antigens which though somewhat related to, are clearly antigenically distinct from, those of short ragweed pollen. Yunginger and Gleich (Ref. 41), using radioimmunoassay techniques, and Leiferman, Gleich, and Jones (Ref. 158), using radioallergosorbent techniques, have shown both cross-reactivity and antigenic differences between southern ragweed and short ragweed (Refs. 41 and 158), giant ragweed (Ref. 158), western ragweed (Refs. 41 and 158). *Franseria* (Refs. 41 and 158), *Iva* (Ref. 158), *Xanthium* (Ref. 158), and *Artemisia* (Ref. 158). There is evidence of an antigen in southern ragweed pollen which cross-reacts slightly with antigen E of short ragweed pollen, but which is clearly antigenically distinct (Ref. 41).

Effectiveness of southern ragweed pollen extracts. (1) *Skin test diagnosis.* The Panel found no controlled studies indicating that southern ragweed pollen extracts are effective for skin test diagnosis of patients with southern ragweed pollinosis.

(2) *Immunotherapy.* The Panel found no controlled studies indicating that immunotherapy with southern ragweed pollen extracts will reduce symptoms of southern ragweed pollinosis or will induce changes in specific IgG or IgE antibodies.

Recommendations. The Panel recommends that southern ragweed pollen extract be placed in Category IIIA for both skin test diagnosis and immunotherapy.

d. *Western ragweed pollen extracts. Ambrosia psilostachya* or western ragweed is widely distributed in, and most abundant in, the Great Plains, but occurs sporadically in the far West and east of the Mississippi. It may be an important contributor to the air-borne pollen load (Refs. 43 through 45). The pollen may cause hay fever and asthma (Refs. 42 through 45, 64, and 151). The pollen of western ragweed cross-reacts with that of short ragweed so that a patient sensitive to one will usually react to the other (Refs. 43, 44, and 91). However, antigenic differences are recognized, and western ragweed pollen has antigens which though somewhat related are clearly antigenically distinct from those of short ragweed pollen.

Wodehouse (Ref. 46) and Prince and Secrest (Ref. 48), using passive transfer

neutralization techniques, Yunginger and Gleich (Ref. 41), using radioimmunoassay techniques, and Leiferman, Gleich, and Jones (Ref. 158), and Bernstein et al. (Ref. 91), using radioallergosorbent techniques, have shown both cross-reactivity and antigenci differences between western ragweed and short ragweed (Refs. 41, 46, 48, 91, and 158), giant ragweed (Refs. 41, 48, 91, and 158), southern ragweed (Refs. 41 and 158), *Franseria* (Refs. 41, 46, 91, and 158), *Iva* (Refs. 41, 48, and 158), *Xanthium* (Refs. 41 and 158), and *Artemisia* (Refs. 41, 46, and 158).

There is evidence of small quantities of an antigen in some, but not all, western ragweed pollen extracts which is essentially identical to antigen E and which may be due to contamination of these extracts by trace amounts of short ragweed (Ref. 41).

Effectiveness of western ragweed pollen extract. (1) *Skin test diagnosis.* The Panel found one reported study of the diagnostic use of western ragweed pollen extracts in patients with ragweed pollinosis. Prince and Secrest (Ref. 48) reported 44 patients with hay fever symptoms in the ragweed pollen season. Fifteen of these had positive skin reactions to western ragweed pollen extract. The others reacted to short or giant ragweed or marsh elder (*Iva ciliata*). Two of the 15 reacted to western ragweed pollen extract only; the 13 others reacted also to one or more of the other tested ragweed family (short and giant ragweed, and marsh elder) pollen extracts. Passive transfer tests were positive with five of five tested sera. No eye, nose, or bronchial challenge, leukocyte histamine release, or radioallergosorbent tests were reported. Negative skin tests in nonallergic controls were obtained in the 27 recipients of the passive transfer tests. Western ragweed pollen extract was made by the authors. Western ragweed pollen was defated with petrolic ether and extracted with "bicarbonate extracting fluid."

(2) *Immunotherapy.* The Panel found no controlled studies indicating that immunotherapy with western ragweed pollen extracts will reduce symptoms of western ragweed pollinosis, or will induce changes in anti-western ragweed pollen IgG or IgE antibodies. However, considering the close immunologic relationships between western and short ragweed, the effectiveness of such immunotherapy would be expected.

Recommendations. The reported results of skin testing with western ragweed pollen extracts indicate that these extracts are effective for skin test diagnosis. The Panel found only circumstantial evidence indicating that these extracts are effective for immunotherapy. The Panel recommends that western ragweed pollen extract be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

e. *Franseria or false ragweeds.* *Franseria confertiflora* (syn. *Ambrosia Confertiflora* or *F. tenuifolia*) or slender ragweed is the prototype pollen. Close relatives are *F. acanthicarpa* or bur ragweed, *F. Deltoidea* or rabbit bush, *F. dumosa* or burroweed, and *F. ambrosioides* or canyon ragweed. Some of these false ragweeds, particularly the last three species, bloom in the spring in the arid regions of the southwest and may cause spring hay fever symptoms in ragweed-sensitive patients. Most also pollinate in the usual fall ragweed pollinating season. The false ragweeds grow in warm dry districts from the western part of the Mississippi Valley to Colorado, Nevada, and southern California, and south to Texas. Throughout most of their range, they appear to be less important than other ragweeds, but in parts of Arizona they are considered to be among the most important causes of hay fever and increasing in abundance (Refs. 42 through 45, 64, and 151).

The pollen of slender ragweed cross-reacts with that of short ragweed so that a patient sensitive to one usually will react to the other (Refs. 43 through 45). However, antigenic differences are recognized and slender ragweed pollen has some antigens which are related and some which may be distinct from those of short ragweed pollen.

Wodehouse (Ref. 46) in passive transfer neutralization experiments found that "slender" and "bur" ragweed pollen extracts would completely neutralize each other, completely neutralize western and short ragweed and partially neutralize sage brush. Leiferman, Gleich, and Jones (Ref. 158), using radioallergosorbent techniques have shown considerable cross-reactivity between both false and slender ragweed and giant, short, and western ragweed pollen extracts and slight cross-reactivity between false and slender ragweed and cocklebur (*Xanthium commune*) and wormwood (*Artemisia annua*) pollen extracts. Bernstein et al. (Ref. 91), using radioallergosorbent techniques have demonstrated considerable cross-reactivity between short, giant, and western ragweed and false ragweed (*F. acanthicarpa*) pollen extracts. Yunginger and Geich (Ref. 41) found evidence of a small amount of an antigen is false ragweed which cross-reacted with antigen E. There was a lesser amount of cross-reacting antigens in slender ragweed pollen extracts. Bernstein et al. (Ref. 91) found concentrations of antigen E in an extract of false ragweed (*F. acanthicarpa*) higher than that in a short ragweed pollen extract. The exact levels were not given.

Effectiveness for skin test diagnosis. No controlled studies were found indicating that slender ragweed pollen extracts are effective for skin test diagnosis of patients with slender ragweed pollinosis.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with slender ragweed pollen extracts will reduce symptoms of slender ragweed pollinosis better than placebo, or will induce changes in anti-slender ragweed pollen IgG or IgE antibodies.

Recommendations. The Panel recommends that slender ragweed pollen extract be placed in Category IIIA for both skin test diagnosis and immunotherapy.

f. *Other Ambrosiae.* Most of the other *Ambrosiae* are listed in Table 1. These are usually of much less importance than the species previously discussed but may be locally important as producers of pollen which cause hay fever in North America, South America Europe, and Africa.

It is generally stated that these pollens cross-react with the pollen of short ragweed so that a patient sensitive to one will usually react to the other (Refs. 43 and 44). However, the experience with the better studied species of ragweed previously discussed suggest that these species also will be found to contain antigens which though somewhat related are clearly antigenically distinct from those of short ragweed.

There is no standard of potency for these extracts such as antigen E affords for short ragweed pollen extract. The relationships of antigens in these pollens to antigen E have not yet been studied.

Effectiveness for skin test diagnosis. The Panel found no controlled studies indicating that these extracts are effective for skin test diagnosis of patients with pollinosis.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with these pollen extracts will reduce symptoms of pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. The Panel recommends that the other *Ambrosiae* pollen extracts be placed in Category IIIA for both skin test diagnosis and for immunotherapy.

g. *Iva or marsh elders.* Table 1 lists 10 *Iva* species. These occur over most of the United States. The most important species, *Iva xanthifolia* (syn. *Cyclachaena xanthifolia*) also known as burweed marsh elder, prairie ragweed, horseweed, and careless weed, extends from Illinois to Saskatchewan and Idaho and southward to New Mexico, Texas, and Missouri. It produces enormous amounts of pollen in July and August, sometimes producing more than short ragweed, and is one of the most important causes of hay fever throughout much of its range (Refs. 42 through 45, 64, and 151).

Marsh elder pollen cross-reacts with that of short ragweed so that a patient sensitive to one will usually react to the other (Refs. 43, 44, 48, and 49). However, antigenic differences are recognized and *Iva* has some antigens which are related and some which may be distinct from those of short ragweed (Refs. 41, 48, and 158). Prince and Secrest (Ref. 48), using passive transfer neutralization techniques, Yunginger and Gleich (Ref. 41), using radioimmunoassay techniques, and Leiferman, Gleich, and Jones (Ref. 158), using radioallergosorbent techniques, have demonstrated both cross-reactivity and antigenic differences between *Iva* and short ragweed (Refs. 41, 48, and 158), giant ragweed (Refs. 48 and 158), southern ragweed (Ref. 158), western ragweed (Refs. 48 and 158), *Franseria* (Ref. 158), *Xanthium* (Refs. 41 and 158), and *Artemisia* (Refs. 41 and 158). There is evidence of small quantities of an antigen in some but not all marsh elder extracts which is essentially identical to antigen E in short ragweed pollen and which may be due to contamination of these extracts by trace amounts of short ragweed (Ref. 41).

Effectiveness for skin test diagnosis. The Panel found one reported study of the diagnostic use of *Iva ciliata* (marsh elder) pollen extracts in patients with marsh elder pollinosis. Prince and Secrest (Ref. 48) reported 44 patients with hay fever symptoms in the fall pollen season. Thirty-two of these had positive skin reactions to marsh elder pollen extract. The others reacted to short, giant, or western ragweed pollen extract. Four of the 32 reacted to marsh elder pollen extract only; the others reacted also to one or more of the tested ragweed (short, giant, and western) pollen extracts. Passive transfer tests were positive with 5 of 5 tested sera. No eye, nose, or bronchial challenge, leukocyte histamine release, or radioallergosorbent tests were reported. Negative skin tests in nonallergic controls were obtained in the 27 recipients of the passive transfer tests. Marsh elder pollen extract was made by the authors. Marsh elder pollen collected by the authors was defatted with petroleum ether and extracted with "bicarbonate extracting fluid."

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with marsh elder pollen extracts will reduce symptoms of marsh elder pollinosis better than placebo, or will induce changes in anti-marsh elder pollen IgG or IgE antibodies.

Recommendations. The reported results of skin testing with marsh elder pollen extracts indicate that these extracts are effective for skin test diagnosis. The Panel found only circumstantial evidence indicating that these extracts are effective for immunotherapy. The Panel recommends that marsh elder pollen extracts be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

h. *Xanthium, or cocklebur.* Cocklebur occurs in distrubed soil over much of the world. These plants may be locally abundant in many States of the U.S.A., but pollen production is usually small, and their importance as causes of hay fever is minor (Refs. 42 through 45, 64 and 151).

The pollen of cocklebur cross-reacts with that of short ragweed so that a patient sensitive to one usually will react to the other (Refs. 43 through 45). However, antigenic differences are recognized and cocklebur pollen has some antigens which are related and some which may be distinct from those of short ragweed pollen.

Wodehouse (Ref. 46) in passive transfer neutralization experiments found that cocklebur pollen extracts contained both common and distinct antigens when compared with short ragweed, marsh elder, burweed marsh elder, and sage brush pollen extracts. Leiferman, Gleich, and Jones (Ref. 158), using radioallergosorbent techniques, have shown slight cross-reactivity between cocklebur and short, giant, western, false, and slender ragweed and wormwood (*Artemisia annua*) pollen extracts. Yunginger and Gleich (Ref. 41) found some evidence of an antigen in cocklebur which cross-reacted slightly with antigen E, but was clearly antigenically distinct.

Effectiveness for skin test diagnosis. The Panel found no controlled studies indicating that cocklebur pollen extracts are effective for skin test diagnosis of patients with cocklebur pollinosis.

Effectiveness for immunotherapy. The Panel found no controlled studies on immunotherapy with cocklebur pollen extracts.

Recommendations. The Panel found only circumstantial evidence indicating that cocklebur extract is effective for skin test diagnosis and immunotherapy of cocklebur pollinosis and recommends that cocklebur pollen extract be placed in Category IIIA both for skin test diagnosis and for immunotherapy.

i. *Artemisia.* Artemisia, the sage brushs, mugworts, and wormwoods are primarily found in the western prairies and mountains, but some species may be found in almost every part of North America. *Artemisia tridentata* or common sagebrush is the most abundant and important of the artemisias as a cause of hay fever, and in many places greatly outranks the ragweeds in this regard.

Other species are sand sagebrush (*Artemisia filifolia*) of the western edge of the great plains, coastal sagebrush (*Artemisia californica*) of the coast ranges of California, prairie sage (*Artemisia ludoviciana*) and pasture sage (*Artemisia caudata*) which is locally abundant on the shores of the Great Lakes. There are many other less common species including annual sage (*Artemisia annua*) which has been introduced from Asia and has become established in Tennessee and surrounding states. Artemisias are found at various latitudes and elevations with pollination occurring from June through October although most species shed their pollen in September (Refs. 42 through 45, 64, and 151).

The pollens of the artemisias cross-react with that of short ragweed so that a patient sensitive to one will usually react to the other (Refs. 43 through 45). However, antigenic differences are recognized, and artemisias have antigens which though somewhat ralated are still antigenically distinct from those of short ragweed pollen (Refs. 41 and 46).

Wodehouse (Ref. 43) states:

> Among the artemisias there appears to be closer antigenic similarity than in any other group, except possibly some of the grasses. Thus the following seven species, coast sagebrush (*A. californica*), common mugwort (*A. vulgaris*), California mugwort (*A. heterophylla*), green sage (*A. ludoviciana*), pasture sage (*A. frigida*), silvery wormwood (*A. filifolia*) and sagebrush (*A. tridentata*) were compared by reagin neutralization (Ref. 46) and found to be reciprocally neutralizing. That is to say, a sagebrush-sensitive patient was found to be equally sensitive to the pollen of all seven species, and the serum of this patient when neutralized by the pollen of sagebrush was found by passive transfer to be neutralized to the other six, and the reverse was equally true. This is very nearly

if not unique, the criterion of allergic identity of these seven species. And since they represent all four sections of the same genus, it is more than likely that other species would prove the same. This being the case, the pollen of any one species could serve for the diagnoses and treatment of sensitivity to the whole group.

There is evidence of small quantities of an antigen in some but not all artemisia extracts which is essentially identical to antigen E and which may be due to contamination of these extracts by trace amounts of short ragweed (Ref. 41).

Effectiveness for skin test diagnosis. The Panel found two reported studies of the diagnostic use of artemisia pollen extracts in patients with artemisia pollinosis.

Wodehouse (Ref. 161) reported one patient with hay fever in the sagebrush pollen season who had positive direct skin and passive transfer reactions to sagebrush pollen extracts. Negative skin reactions to sagebrush pollen extracts were obtained in one of one control patients without evidence of pollinosis. No eye, nose or bronchial challenge, leukocyte histamine release, or radioallergosorbent tests were reported. Extracts were made by the author. The pollen was extracted with Coca's solution and standarized by the total nitrogen method. Patients were scratch tested with extract containing 20,000 nitrogen units per cc.

Dumm and Zarate (Ref. 162) reported five patients with pollinosis (four with hay fever and asthma, one with hay fever alone) in the season of pollination of *Artemisia verlotorum* who had positive direct skin and passive transfer reactions with *A. verlotorum* pollen extracts. Nasal challenge tests with dry *A.verlotorum* pollen were positive in all. No eye or bronchial challenge, leukocyte histamine release, or radioallergosorbent tests were reported.The source of the extracts and details of skin testing were not given.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with artemisia pollen extracts will reduce symptoms of artemisia pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. The reported results of skin testing with artemisia pollen extracts suggest that these extracts are effective for skin test diagnosis, but only circumstantial evidence was found indicating that these extracts are effective for immunotherapy. The Panel recommends that artemisia pollen extracts be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

j. *Other wind pollinated Compositae.* Table 1 lists other wind pollinated *Compositae* which have not yet been discussed. More information on the geographic distribution of these can be found in standard references (Refs. 43 through 45).

It is generally stated that these pollens cross-react with the pollen of short ragweed so that a patient sensitive to one will usually react to the other (Refs. 43 and 44). However, the experience with the better studies species of *Compositae* previously discussed suggest that these species also will be found to contain antigens which, though somewhat related, are clearly antigenically distinct from those of short ragweed.

There is no standard of potency for these extracts such as antigen E affords for short ragweed pollen extract. The relationships of antigens in these pollens to antigen E have not been studied.

Effectiveness for skin test diagnosis. The Panel found no controlled studies indicating that these extracts are effective for skin test diagnosis.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with these pollen extracts will reduce symptoms of pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. The Panel found only circumstantial evidence indicating that these pollen extracts are effective for skin test diagnosis and immunotherapy of pollinosis and recommends that extracts of other wind pollinated *Compositae* pollen be placed in Category IIIA both for skin test diagnosis and immunotherapy.

k. *Insect pollinated Compositae.* As a general rule, the pollens of the insect pollinated *Compositae* are not buoyant enough to be a factor in pollinosis. Nevertheless, the plants may be very abundant locally, and patients in close contact may be sufficiently exposed to their pollen to have hay fever. Some but not all of these plants are listed in Table 1 and include such common ones as sunflower, goldenrod, aster, chrysanthemum, pyrethrum, dahlia, marigold, zinnia, cosmos, sneezeweed, dog fennel, and dandelion.

It is stated that the pollens of insect pollinated *Compositae* cross-react with, short ragweed pollen so that a patient sensitive to one will usually react to the others (Refs. 43 through 45). However, antigenic differences are recognized for some and are probably present for all. Walker (Ref. 94) noted that patients with positive skin tests to short ragweed pollen frequently had skin reactions to strong concentrations of sunflower, golden glow, daisy, and goldenrod, but that skin reactions were usually negative when weak concentrations were used. Bernton (Ref. 164) noted that patients with positive skin reactions to short ragweed pollen usually had positive skin reactions to cosmos. Vaughan and Crockett (Ref. 51) noted that 30 of 100 patients with skin reactions to ragweed had positive skin reactions to goldenrod and that "in the majority of instances" the patients with positive skin reactions to goldenrod had positive skin reactions to ragweed. Simon (Ref. 63), using passive transfer neutralization techniques demonstrated cross-reactions between short ragweed, giant ragweed, goldenrod, dandelion, sunflower, and cosmos.

Feinberg (Ref. 50) noted that 104 of 225 patients with cutaneous reactions to ragweed pollen had cutaneous reactions to commercial pyrethrum which is derived from pyrethrum flowers which bear pollen.

Effectiveness for skin test diagnosis. The Panel found no well-controlled studies which establish the effectiveness of allergenic extracts of the various insect pollinated *Compositae* pollens for skin test diagnosis of patients with hay fever and/or asthma after inhalation of these pollens.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with these pollen extracts will reduce symptoms of pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. Only circumstantial evidence was found indicating that these various insect pollinated *Compositae* pollen extracts are effective for skin test diagnosis and immunotherapy of pollinosis, and it is recommended that extracts of insect pollinated *Compositae* pollen be placed in Category IIIA both for skin test diagnosis and immunotherapy.

3. *Amaranthaceae Family*—a. *Amaranthus (amaranth or pigweed).* *Amaranthus retroflexus* (common, rough, or redroot pigweed) is the prototype *Amaranthus* species. It is common in cultivated or waste soil throughout North America and in Europe and sheds some pollen in late summer which may cause hay fever. *Amaranthus Palmeri* (carelessweed, Palmer's amaranth) is found in Missouri, Kansas, Oklahoma, Texas, Arizona, New Mexico, and California, sheds much pollen between June and September, and is an important cause of hay fever where abundant. *Amaranthus spinosus* (spiny amaranth) occurs in waste ground from Maine to Minnesota

and southward. In the western and southern regions of its range where abundant, it may cause hay fever (Refs. 42 through 45, 64, and 151).

It is generally stated that the pollens of the various species of the amaranths cross-react with each other and with western waterhemp or *Acnida tamariscina* (Refs. 43, 44, 122, 142, 149, and 151). Sellers and Adamson (Ref. 122), using passive transfer desensitization or exhaustion techniques, and Wodehouse (Ref. 142), using gel diffusion techniques, have shown that *Amaranthus spinosus, Amaranthus Palmeri, Amaranthus retroflexus,* and *Acnida tamariscina* contain identical antigens in nearly the same proportions. They have further shown that these same four *Amaranthaceae* pollens contain antigens which are somewhat related to but clearly distinct from those of the *Chenopodaceae* including Russian thistle (*Salsola pestifer*), burning bush (*Kochia scoparia*), lamb's-quarters (*Chenopodium album*), shadscale (*Artiplex canescens*), and annual saltbush (*Atriplex Wrightii*),

Sellers and Adamson (Ref. 122) noted that all of 36 patients who had positive reactions to scratch tests with 1:100 w/v glycerin saline extracts of any of four amaranth species (spiny amaranth, careless weed, pigweed, and western waterhemp) had positive skin tests to the others, and in all but one instance to Russian thistle, and in all but three to lamb's-quarters. In commenting on these data, Durham (Ref. 151) stated:

> Botanically the chenopods (Chenopodiaceae) and the amaranths (Amaranthaceae) are closely related. Considerable evidence has been found that patients sensitive to the pollen of any species of the several genera belonging to these two families are usually more or less sensitive to the pollen of any or all species of both families. Thus for practical purposes the allergist may regard the members of these two families as a working unit.

Effectiveness for skin test diagnosis. The Panel found three reports of the diagnostic use of amaranth pollen extracts in patients with amaranth pollinosis.

Sellers and Adamson (Ref. 122) described 36 patients with amaranth pollen hay fever who had positive skin tests to amaranth pollen extracts. Skin tests with the amaranth pollen extracts in two nonallergic patients were negative. Passive transfer tests were positive with the sera of all nine of these patients. No eye, nose, or bronchial challenge, radioallergosorbent, or leukocyte histamine-release tests were reported. The extracts were made by the authors and were glycerin saline extracts produced by extracting 1 gram of dry pollen with 100 cc. of "fluid". Skin tests were done by the scratch method except for a "few tests made intradermally for corroboration."

Heinberg (Ref. 174) described one patient with hay fever during the amaranth pollen season who had a positive skin reaction to spiny amaranth pollen extract. No skin tests in nonallergic patients were described. No eye, nose, or bronchial challenge, passive transfer, leukocyte histamine release, or radioallergosorbent tests were reported. The source of and manufacturing methods for the extracts were not given.

Lindenbaum (Ref. 110) reported nine patients with a history of seasonal hay fever and/or asthma during the amaranth pollen season who had positive skin reactions to amaranth pollen. No skin tests in nonallergic controls were described. No eye, noise, and bronchial challenge, passive transfer, leukocyte histamine-release or radioallergosorbent tests were reported. The source of materials and manufacturing methods for the extracts were not described.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with Ameranth species pollen extracts.

Recommendations. The reported results of skin testing with amaranth pollen extracts indicate that these extracts are effective for skin test diagnosis, but only circumstantial evidence was found indicating that these extracts are effective for immunotherapy. The Panel recommends that extracts of these three amaranthus pollens be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

b. *Acnida or water hemp. Acnida tamariscina* or western water hemp is the prototype species. It is abundant in the prairie region from South Dakota, Nebraska, and Kansas, west to New Mexico, south to Texas, and east to Indiana. It produces large amounts of airborne pollen in the period from July to September which may cause hay fever and asthma (Refs. 42 through 45, 64, 151, and 175).

It is generally stated that the pollens of the western water hemp and of the various species of the amaranths cross-react with each other (Refs. 43, 44, 122, 142, 149, and 151). Sellers and Adamson (Ref. 122), using passive transfer neutralization techniques and Wodehouse (Ref. 142), using gel diffusion techniques have shown that western water hemp, spiny amaranth (*Amaranthus spinosus*), careless weed (*Amaranthus Palmeri*), and pigweed (*Amaranthus retroflexus*) contain identical antigens in nearly the same proportions. They have further shown that these same four *Amaranthaceae* pollens contain antigens which are somewhat related to but clearly distinct from those of the *Chenopodiaceae* including Russian thistle (*Salsola pestifer*), burning bush (*Kochia scoparia*), lamb's-quarters (*Chenopodium album*), shadscale (*Atriplex canescens*) and annual saltbush (*Atriplex Wrightii*).

Sellers and Adamson (Ref. 122) noted that all of 36 patients who had positive reactions to scratch tests with 1:100 w/v glycerinated saline extracts of any of four amaranth species (spiny amaranth, careless weed, pigweed, and western water hemp) had positive skin tests to the other, and in all but one instance to Russian thistle, and in all but three to lamb's-quarters. Durham (Ref. 151) noted the antigenic similarity of the amaranthsand chenopods.

Effectiveness for skin test diagnosis. The Panel found two reported studies of the diagnostic use of water hemp pollen extracts in patients suspected of having water hemp pollinosis.

Sellers and Adamson (Ref. 122) reported 36 patients with hay fever in the western water hemp pollen season who had positive skin reactions to western water hemp extracts. Passive transfer tests were positive with the sera of all nine of the patients who were tested. Negative skin reactions to western water hemp pollen extracts were obtained in two of two control patients without evidence of western water hemp pollinosis. No eye, nose or bronchial challenge, leukocyte histamine release, or radioallergosorbent tests were reported. Extracts were made by the authors. They were glycerin saline extracts prepared by extracting one gm. of dried pollen with 100 cc. of "fluid." Skin tests were done by the scratch method except for a "few tests made intradermally for corroboration."

Balyeat and Stemen (Ref. 175) reported 116 patients with hay fever in the western water hemp pollen season who had positive skin reactions to western water hemp pollen extracts. They reported no negative skin reactions to western water hemp pollen extracts in control patients without evidence of western water hemp pollinosis. No eye, nose, or bronchial challenge, leukocyte histamine release, passive transfer, or radioallergsorbent tests were reported. The source of materials and the manufacturing methods for the western water hemp pollen extracts were not described.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with *Acnida tamariscina* pollen extracts.

Recommendations. The reported results of skin testing with western water hemp extract indicate that it is effective for skin test diagnosis but only circumstantial evidence was found indicating that it is effective for immunotherapy. The Panel recommends that western water hemp pollen extract be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

4. *Chenopodiaceae Family*—a. *Salsola pestifer* or *salsola kali var. tenuifolia (Russian thistle or tumble weed).* *Salsola pestifer* is common throughout the prairies, Great Basin, and Rocky Mountain areas in the United States. It sheds large amounts of pollen between June and September and may cause hay fever (Refs. 42 through 45, 64, and 151).

Sellers and Adamson (Ref. 122) noted that all of 35 patients who had positive reactions to scratch tests with 1:100 w/v glycerin saline extracts of Russian thistle also had positive skin reactions to *Amaranthus spinosus* (spiny amaranth), *Amaranthus palmeri* (careless weed), *Amaranthus retroflexus* (pigweed), and *Acnida tamariscina* (western water hemp) pollen extracts. All but three also had positive skin reactions to *Chenopodium album* (lamb's-quarters) pollen extracts. Using passive transfer desensitization or exhaustion techniques, they found that sites desensitized to the four amaranth pollen extracts were also desensitized to Russian thistle and lamb's-quarters pollen extracts but that desensitization with Russian thistle pollen extracts did not desensitize to the four amaranth pollen extracts and in only 75 percent of experiments desensitized to lamb'squarters pollen extracts.

Wodehouse (Ref. 142) using gel diffusion techniques, has shown that Russian thistle pollen shares many but not all antigens with burining bush (*Kochia scoparia*) shares a few with careless weed, and less with lamb's-quarters, annual saltbush, and shadscale (*Atriplex canescens*). He concluded that by this technique there was much less similarity between the members of the chenopod group than between those f the amaranth group. He also showed that there were both common and distinct antigens in Russian thistle, careless weed, spiny amaranth, pigweed, and western water hemp.

Durham's statement (Ref. 151) quoted earlier also notes the antigenic similarity of the chenopods and amaranths.

Effectiveness for skin test diagnosis. The Panel found two reported studies of the diagnostic use of Russina thistle pollen extracts in patients suspected of having Russian thistle pollinosis.

Sellers and Adamson (Ref. 122) reported 36 patients with hay fever in the Russian thistle pollen season of whom 35 had positive skin tests to Russian thistle pollen extracts. Passive transfer tests were positive with the sera of all nine of the patients who were tested. Negative skin reactions to Russian thistle pollen extracts were obtained in two of two control patients without evidence of Russian thistle pollinosis. No eye, nose, or bronchial challenge, leukocyte histamine release, or radioallergosorbent tests were reported. Extracts were made by the authors. They were glycerin saline extracts prpared by extracting one gram of dried pollen with 100 cc. of "fluid." Skin tests were done by the scratch method except for a "few tests made intradermally for corroboration."

Wodehouse (Ref. 160) reported three patients with hay fever in the Russian thistle pollen season who had positive skin tests to Russian thistle pollen extracts. Passive transfer tests were positive using the sera from all three of the patients. Negative skin reactions to Russian thistle pollen extracts were obtained in at least two nonallergic controls. No eye, nose, or bronchial challenge, leukocyte histamine release, or radioallergosorbent tests were reported. The source of materials and the manufacturing method for the extracts were not described.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with Russian thistle pollen extracts will reduce symptoms of Russian thistle pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. The reported results of skin testing with Russian thistle pollen extract indicate that it is effective for skin test diagnosis but only circumstantial evidence was found indicating that it is effective for immunotherapy. The Panel recommends that *Salsola pestifer* pollen extract be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

b. *Kochia scoparia (kochia, burning bush, fire bush, summer cypress, or belvedere).* Kochia is a native of Europe and Asia, which has been transported to America and has become naturalized throughout much of the northern midwest and Great Plains area in the states between the Rocky Mountains and Great Lakes particularly Iowa, South Dakota, Wyoming, Colorado, Wisconsin, and Minnesota. It sheds large quantities of pollen between July and September which may cause hay fever (Refs. 43 through 45, 64, 151, and 176).

Wodehouse (Ref. 160), using a passive transfer neutralization technique showed that kochia pollen extracts would neutarlize reciprocally Russian thistle (*Salsola pestifer*), annual saltbush (*Atriplex Wrightii*) pollen extracts using one patient's serum; Russian thistle, lamb's-quarters (*Chenopodium album*), annual saltbush, and careless weed (*Amaranthus Palmeri*) pollen extracts using another; and would not neutralize Russian thistle pollen extracts using a third serum.

Wodehouse (Ref. 142), using gel diffusion techniques, has shown that kochia pollen shares many, but not all, antigens with Russian thistle; shares a few with careless weed, pigweed (*Amaranthus retroflexus*), and spiny Amaranth (*Amaranthus spinosus*); and shares none with western water hemp (*Acnida tamariscina*).

Durham's statement (Ref. 151) quoted earlier also notes the antigenic similarity of the amaranths and chenopods.

Effectiveness for skin test diagnosis. The Panel found adequate evidence of the allergenicity of kochia pollen extract (Refs. 142 and 151 discussed above) and one reported study of the diagnostic use of kochia pollen extracts in patients suspected of having kochia pollinosis.

Wodehouse (Ref. 160) reported three patients with hay fever in the kochia pollen season who had positive skin tests to kochia pollen extracts. Passive transfer tests were positive using the sera from all three of the patients. Negative skin reactions to kochia pollen extracts were obtained in at least two nonallergic controls. No eye, nose, or bronchial challenge, leukocyte histamine release, or radioallergosorbent tests were reported. The source of materials and the manufacturing method for the extracts were not described.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with kochia pollen extracts will reduce symptoms of Russian thistle pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. The Panel recommends that extract of kochia pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

c. *Chenopodium album.* (*Chenopodium album* or lamb's-quarters is a native of Europe, but is now naturalized throughout North America. The plants pollinate from July to mid-September, and though entirely wind-pollinated, do not shed much pollen. However, where the plants are very abundant, there may be sufficient pollen to cause hay fever (Refs. 42 through 45, 64, 125, and 151). *Chenopodium paganunum Reichenb* or summer blooming lamb's-quarters is also found through much of the United States and has been described as a producer of abundant, buoyant pollen from June to October which may cause hay fever at least in Oklahoma (Ref. 126).

Sellers and Adamson (Ref. 122) noted that all of 33 patients who had positive reactions to scratch tests with 1:100 w/v glycerin saline extracts of lamb's-quarters pollen extracts also had positive skin reactions to *Amaranthus spinosus* (spiny amaranth), *Amaranthus Palmeri* (cardless weed), *Amaranthus retroflexus* (pigweed), and *Acnida tamariscina* (western water hemp) pollen extracts. All but possibly one also had positive skin reactions to *Salsola pestifer* (Russian thistle) pollen extracts. Using passive transfer desensitization or exhaustion techniques, they found that sites desensitized to the four amaranth pollen extracts were also desensitized to lamb's-quarters and Russian thistle pollen extracts but that desensitization with lamb's-quarters pollen extracts did not desensitize to the four amaranth pollen extracts and in only 50 percent of experiments desensitized to Russian thistle pollen extracts.

Wodehouse (Ref. 160), using a passive transfer neutralization technique, showed that lamb's-quarters pollen extracts would neutralize reciprocally burning bush (*Kochia scoparia*), annual saltbush (*Atriplex Wrightii*), and careless weed pollen extracts using one patient's serum, but would not neutralize Russian thistle pollen extracts using two other patient's sera.

Wodehouse (Ref. 142), using gel diffusion, showed that lamb's-quarters pollen extract shares a few antigens with Russian thistle pollen extract but is mainly distinct.

Durham's statement (Ref. 151) quoted earlier also notes the antigenic similarity of the chenopods and amaranths.

Effectiveness for skin test diagnosis. The Panel found four reported studies of the diagnostic use of lamb's-quarters pollen extracts in patients suspected of having lamb's-quarters pollinosis.

Sellers and Adamson (Ref. 122) reported 36 patients with hay fever in the lamb's-quarters pollen season of whom 33 had positive skin tests to lamb's-quarters pollen extracts. Passive transfer tests were positive with the sera of all nine of the patients who were tested. Negative skin reactions to lamb's-quarters pollen extracts were obtained in two of two control patients without evidence of lamb's-quarters pollinosis. No eye, nose, or bronchial challenge, leukocyte histamine release, or radioallergosorbent tests were reported. Extracts were made by the authors. They were glycerin saline extracts prepared by extracting 1 gram of dried pollen with 100 cc. of "fluid." Skin tests were done by the scratch method except for a "few tests made intradermally for corroboration."

Wodehouse (Ref. 160) reported three patients with hay fever in the lamb's-quarters pollen season who had positive skin tests to lamb's-quarters pollen extracts. Passive transfer tests were positive using the sera from all three of the patients. Negative skin reactions to lamb's-quarters pollen extracts were obtained in at least two nonallergic controls. No eye, nose, or bronchial challenge, leukocyte histamine release, or radioallergosorbent tests were reported. The source of materials and the manufacturing method for the extracts were not described.

Homan (Ref. 125) noted that lamb's-quarters pollen is abundant in the Ohio Valley area in the late summer season when ragweed is also pollinating. He found that when all patients with late summer pollinosis symptoms were skin tested with both lamb's-quarters and ragweed pollen extracts that about 20 percent of the patients who reacted to ragweed pollen also reacted to lamb's-quarters pollen extracts. No eye, nose, or bronchial challenge, leukocyte histamine release, or radioallergosorbent tests were reported. The source of materials and manufacturing method for the extracts were not described.

Blue (Ref. 126) reported that "some" patients who had positive skin reaction to summer blooming lamb's-quarters extract also had positive "mucus membrane tests" manifested by lacrimation, sneezing, and general hay fever symptoms. Negative skin tests in nonallergic controls were obtained in 61 patients using summer blooming lamb's-quarters pollen extracts, and in 143 patients using *Chenopodium album* extracts. The source of materials and the manufacturing methods for the extracts were not described.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with lamb's-quarters pollen extracts will reduce symptoms of lamb's-quarters pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. The Panel recommends that extract of lamb's-quarters pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

d. *Atriplex or saltbush. Atriplex Wrightii* (annual saltbush) is the prototype species and is found in New Mexico, Arizona, and adjoining Mexico. Other species include *Atriplex canescens* (shadscale or wingscale), *Atriplex confertifolia* (spiny saltbush), *Atriplex polycarpa* (allscale), *Atriplex lentiformis* (lenscale), *Atriplex argente* (silverscale), and *Atriplex semibacatta* (fleshscale) which live in various parts of the arid southwestern and far western portions of the United States where the soil is alkaline. They flower from early spring to late summer and may produce large amounts of airborne pollen which may cause hay fever (Refs. 43 through 45, 64 and 151).

Wodehouse (Refs. 160) using passive transfer neutralization techniques, showed that annual saltbush pollen extracts would neutralize reciprocally Russian thistle *(Salsola pestifer),* and kochia *(Kochia scoparia)* pollen extracts using one patient's serum; Russian thistle, kochia, lamb's-quarters *(Chenopodium album),* and careless weed *(Amaranthus Palmeri)* pollen extracts using another patient's serum, and Russian thistle pollen extracts using a third patient's serum.

Wodehouse (Ref. 142), using gel diffusion, has shown that shadscale (*Atriplex canescens*) pollen extract contains most, if not all, of the antigens present in annual saltbush pollen (*Atriplex Wrightii*), contains many but not all antigens present in careless weed pollen extract, and contains a few present in Russian thistle pollen extract. Durham's statement about the antigenic similarity of the chenopods and amaranths was mentioned earlier (Ref. 151).

Effectiveness for skin test diagnosis. The Panel found no reported studies of the diagnostic use of *Atriplex* pollen extracts in patients suspected of having *Atriplex* pollinosis.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with *Atriplex* pollen extracts will reduce symptoms of *Atriplex* pollinosis better than placebo or will induce changes in specific IgG or IgE antibodies.

Recommendations. The Panel found only circumstantial evidence indicating that *Atriplex* pollen extracts are

effective and recommends that they be placed in Category IIIA for both skin test diagnosis and immunotherapy.

e. *Beta vulgaris. Beta vulgaris,* or sugar beet, when grown for seeds and allowed to pollinate, sends out vast quantities of very allergenic pollen in May and early June. Seed crops have been reported in Arizona, Utah, and western Texas, where the long growing season and absence of winter kill permit annual crops in contrast to the usual two years required in most of the United States (Refs. 43 through 45, 64, 146, 147 and 148). Since 1956, at least in Utah, pollen exposure in seed production has been reduced through the use of commercial hybrids. For production of these hybrids, approximately 95 percent of the plants are male sterile monogerm beets that produce no pollen. About 5 percent of the plants are pollinators which produce sufficient pollen to fertilize the sterile male plants. This cross-fertilization produces a vigorous hybrid variety, and reduces pollen exposure to the worker (Ref. 146).

Phillips (Ref. 148) reported that most patients with May hay fever in the Phoenix district reacted to both sugar beet pollen and to that of the other chenopods and amaranths. He studied 138 patients with May hay fever. Four reacted to sugar beet and to no other pollen. One hundred and five patients reacted to sugar beet, amranth and Russian thistle. Nineteen reacted to amaranth and Russian thistile, but did not react to sugar beet. Ten patients reacted to grass pollen, but not to sugar beet, amaranth, or Russian thistle. He concluded that sugar beet "has in addition to the group atopen common to the *Chenopodiales* a highly specific atopen of its own."

Effectiveness for skin test diagnosis. The Panel found two reports of the diagnostic use of sugar beet pollen extracts in patients with sugar beet pollinosis.

Dutton (Ref. 147) reported four patients with symptoms of hay fever following exposure to sugar beet pollen who had positive skin tests to sugar beet pollen. He stated that the experience with these four patients was typical of the experience with "a number" of patients. No skin tests were reported in nonallergic controls. No eye, nose, or bronchial challenge, passive transfer, leukocyte histamine release, or radioallergosorbent tests were reported. The source of materials and manufacturing methods for the extracts were not stated.

Phillips (Ref. 148) reported the experience noted above. Negative skin reactions were obtained in 19 nonallergic controls. No eye, nose, or bronchial challenge, leukocyte histamine release, passive transfer, or radioallergosorbent tests were reported. The sugar beet pollen extract was made by the author. The manufacturing method was not reported.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with sugar beet pollen extracts will reduce symptoms of sugar beet pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. The Panel recommends that extract of *Beta vulgaris* pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

5. *Cannabinaceae family*—a. *Cannabis sative or hemp.* This is the prototype *Cannabinaceae* pollen. Hemp is common in the watershed of the Missouri River, in eastern Nebraska and the west edge and north half of Iowa and the adjacent corners of South Dakota, Minnesota, and Kansas. Only in this area has significant air content of hemp pollen been reported (Refs. 43, 44, 52, 53, 64, and 151). The season of hemp pollen dispersal is from early July to early September, and the air at this time of year may be heavily loaded with hemp pollen (Ref. 53). Allergic persons may have hay fever and/or asthma following exposure to the pollen (Refs. 43, 44, 52 and 151).

Marijuana is obtained from hemp plants. However, it is mainly contained in the female pistillate flowers and to a lesser extent in the leaves. The pollen is obtained from the male staminate flowers which occur on different plants from those which bear the female flowers (Ref. 53). Hemp pollen therefore should not contain marijuana, or should contain it only in insignificant amounts (Refs. 43 and 44).

Liskow, Liss, and Parker (Ref. 159) have described a patient who twice had symptoms of hay fever and asthma immediately after smoking a marijuana cigarette. Scratch testing and passive transfer studies confirmed an immunologic basis for her response and indicated that it was related to the cannabinoid and perhaps specifically to the tetrahydrocannabinol component of the marijuana plant. The Panel found no studies indicating whether or not there are common allergens in hemp pollen and marijuana.

No study was found on the antigens in hemp pollen or on their relationships and cross-reactions with antigens in other pollens particularly those in closely related species such as the hop.

Effectiveness for skin test diagnosis. The Panel found only one reported study of the diagnostic use of hemp pollen extracts in patients with hemp pollinosis (Ref. 53). Twenty-eight patients with symptoms of pollinosis at a time when hemp pollen was in the air had positive scratch tests with hemp pollen extract. Eleven of these patients were felt to be allergic to hemp pollen only; 17 were though to be sensitive to hemp and to other pollens. Ninety-one patients had negative skin reactions to hemp pollen extracts. Several hemp pollinosis patients had generalized allergic reactions after skin tests or immunotherapy with hemp pollen extracts. No eye, nose, or bronchial challenge tests or leukocyte histamine release studies were described. Passive transfer and/or radioallergosorbent tests were not done. The source of materials and the manufacturing methods for the hemp pollen extract were not described.

Effectiveness for immunotherapy. No controlled studies were found indicating that immunotherapy with hemp pollen extracts will reduce symptoms of hemp pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. The reported results of skin testing with hemp pollen extract in allergic and nonallergic patients are scanty but indicate that it is effective for skin test diagnosis of hemp pollinosis, and is safe if properly used. It is recommended that extract of hemp pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

b. *Humulus or hop.* Hop is cultivated commercially in America, Europe, and Asia. It has extensively escaped cultivation throughout much of the United States and Canada, east of the Rocky Mountains. Hop pollen has been reported to cause hay fever and/or asthma in Yugoslavia (Ref. 165) and Japan (Ref. 166), and to be a possible cause in the United States (Refs. 43 and 151). The Panel found no study of the antigens in hop pollen or of their relationships and cross-reactions with antigens in other species of pollens.

Effectiveness for skin test diagnosis. The Panel found two reported studies of the diagnostic use of hop pollen extracts in patients suspected of having hop pollinosis.

Cernelc (Ref. 165) reported 65 asthmatic children with a history of increase in symptoms after natural exposure to hop pollen. All had a positive skin test to hop pollen extracts. Fifty-two had positive nasal challenge tests, and 55 had positive bronchial challenge tests with hop pollen extracts. Nasal and bronchial challenge tests were more frequently positive in

patients with strongly positive skin tests. Controls with negative skin reactions to the hop pollen extracts were not reported. No leukocyte histamine release, passive transfer, or radioallergosorbent tests were reported. The hop pollen extracts were made by the Instititue of Immunology, Zagreb, Yugoslavia. Details of skin testing were not given. Bronchial challenge tests were done with increasing concentrations of aqueous extract beginning at a dilution of 1:1000. Nasal challenge tests were done by insufflation of dried pollen extracts.

Horiguchi, Saito, Takayama, Nagatinni, and Saito (Ref. 166) reported one patient with hay fever symptoms and nasal and blood eosinophilia during the hop-pollinating season. Hop plants and pollen were demonstrated in her environment. Intradermal skin test with *Humulus japonica* pollen extract "1:1000" produced a local reaction with pseudopods and exacerbaton of hay fever symptoms. Passive transfer test in a patient who was skin-test negative to the hop extract was positive to a serum dilution of 1:256. Nasal and eye challenge tests with hop pollen were positive. No leukocyte histamine release, bronchial challenge, or radioallergosorbent tests were reported. The source of materials and the manufacturing methods for the hop extract were not stated.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with hop pollen extracts will reduce symptoms of hop pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies.

Cernelc reports in an uncontrolled study that hop pollen extracts may be effective for immunotherapy of hop pollinosis (Ref. 165).

Recommendations. The Panel recommends that extract of *Humulus japonica* pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

6. *Plantaginaceae family*—a. *Plantago or plantain.* The plantain family comprises three general and about 225 species, but only those of the genus *Plantago* are of interest in hay fever studies. The genus consist of about 200 species of wide distribution of which about 20 are native or naturalized in North America. All are wind pollinated, but only English plantain (*Plantago lanceolata*) sheds enough pollen and is sufficiently abundant to cause hay fever. English plantain begins to flower in April or early May and continues to flower throughout the summer, but the bulk of its pollination takes place in May and June, a period almost coinciding with the peak of the grass hay fever season. It is a native of Europe and Asia, but is naturalized thoroughout North America, and is an important cause of hay fever, though in no way comparable with the grasses with which it is generally associated (Refs. 42 through 45, 64 and 151).

Blumstein and Tuft (Ref. 105), using the passive transfer neutralization technique, have shown that plantain antigen is not related to timothy or ragweed antigen. They also reported data showing a common antigenic factor in English and common plantain, but Durham (Ref .64) states that the common plantain used in these experiments was subsequently found by the authors to be mislabeled and was actually English plantain pollen.

Effectiveness for skin test diagnosis. Bernton (Ref. 104) has reported five patients with symptoms of hay fever and/or asthma in the plantain pollen season. All had positive intrademal skin reactions to two pollen units of *P. lanceolata* extract, Negative skin reactions were obtained in 103 controls. No eye, nose, or bronchial challenge, leukocyte histamine release, passive transfer, or radioallergosorbent tests were reported. Plantain pollen extracts were made by the author.

Blumstein and Tuft (Ref. 105) have reported 31 patients with symptoms of hay fever in the plantain pollen season who had positive skin tests to plantain pollen extracts. Eye and/or nose dry pollen challenge tests were positive in 14 of these. Negative skin reactions were obtained in 130 controls. Passive transfer tests were positive in all 14 patients who had positive challenge tests. No bronchial challenge, leukocyte histamine release, or radioallergosorbent tests were reported. The source and manufacturing method for the plantain pollen extract were not given.

Bryant, Burns, and Lazarus (Ref. 97) have reported 72 patients with symptoms of asthma in the plantain pollen season who had positive prick skin tests to plantain pollen extracts. Sixty-nine of these had positive bronchial challenge tests with plantain pollen extracts. All but 2 of the patients with positive bronchial challenge tests had positive radioallergosorbent tests to plantain pollen extracts. Negative skin tests were obtained in 83 healthy controls. No eye or nose challenge, passive transfer, or leukocyte histamine-release tests were reported. Extracts were obtained from Hollister-Stier Laboratories, Inc.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with plantain pollen extracts will reduce symptoms of plantain pollinosis better than placebo, or will induce changes in specific IgG or IgE antibokdies.

Recommendations. The Panel recommends that extract of *Plantago lanceolata* pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

7. *Polygonaceae family*—a. *Rumex acetosella or sheep sorrel.* This is the prototype *Polygonaceae* pollen. Sheep sorrel is a common plant all over the United States (Refs. 43 through 45). Its pollen is found in noteworthy concentrations when collections are done with rotobars. Gravity slide counts underestimate its prevalence because of its small size (Ref. 54). The season of pollen dispersal is between May and June. Allergic persons may have hay fever following exposure to the pollen (Refs. 43 through 45 and 54). The Panel found no study of the antigens in sheep sorrel pollen or of their relationships and cross-reactions with antigens in other species of pollens.

Effectiveness for skin test diagnosis. The Panel found only one reported study of the diagnostic use of sheep sorrel extracts in patients with sheep sorrel pollinosis. Solomon (Ref. 54) reported 30 patients who had strong skin test reactions to sheep sorrel pollen extract. Nineteen of these had positive reactions to nasal provocative testing with sheep sorrel extract; 16 of the 19 had a definite history of nasal symptoms in the sheep sorrel season and 3 did not. Eleven skin test positive patients had negative responses to nasal exposure to sheep sorrel extract; 5 of the 11 had no nasal symptoms during the sheep sorrel season; 6 of the 11 had symptoms during the sheep sorrel season, but had positive nasal reactions to provocation tests with the concomitantly blooming grass pollens in most instances. One hundred and sixty patients had negative skin test reactions to sheep sorrel extracts. Eight of these 160 were subjected to nasal exposure to sheep sorrel extract and negative reactions were obtained in all. No eye or bronchial challenge or leukocyte histamine release studies were described. Passive transfer test was positive with one serum, no radioallergosorbent tests done. Extracts were made by the author by extracting sheep pollen obtained from Greer Laboratories, Inc. with phosphate buffered saline containing either glycerin or phenol. Prick tests were done with 1:5 w/v extract; intradermal and nasal tests were done with 1:500 w/v extract.

Effectiveness for immunotherapy. The Panel found no controlled studies

indicating that immunotherapy with sheep sorrel pollen extracts will reduce symptoms of sheep sorrel pollinosis better than placebo, or will induce changes in specific IgG and IgE antibodies.

Recommendations. The Panel recommends that extract of *Rumex acetosella* pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

b. *Other Rumex pollens. R. crispus* or curley dock, and *R. obtusifolius* or bitter dock are as common and widely distributed as sheep sorrel. They flower from June to August, but shed much less pollen than sheep sorrel (Refs. 43 and 64). Another species, *R. hymenosepalus* the canaigre, occurs in the western United States from California eastward to New Mexico. These three docks are generally accepted to be occasional causes of hay fever, but of less importance in this regard than sheep sorrel (Refs. 43, 45, and 64). The Panel found no study of the antigens and allergens in these other *Rumex* pollens or of their relationships and cross-reactions with antigens and allergens in other species of pollens.

Effectiveness for skin test diagnosis. The Panel found no published studies of the use of these other *Rumex* pollen extracts for skin test diagnosis of pollinosis.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with these other *Rumex* pollen extracts will reduce symptoms of *Rumex* pollinosis or will induce changes in specific IgG or IgE antibodies. The Panel found no statement recommending the use of these other *Rumex* pollen extracts for immunotherapy of *Rumex* pollinosis.

Recommendations. The Panel recommends that extracts of these other *Rumex* pollens be placed in Category IIIA for both skin test diagnosis and immunotherapy.

8. *Gramineae family.* This initial discussion of the *Gramineae* or grass family is concerned with common principles and facts which apply to most or all of the tribes and species of this large family. Subsequent sections will deal with the individual tribes of the grass family and their component species and will emphasize those principles and facts which mainly concern the individual tribe or species.

Specificity. There is considerable evidence of both common and specific antigens in extracts of the various species of grasses. This evidence has been derived from a number of lines of investigation.

a. *Skin testing.* Skin testing has provided evidence of antigens present in most if not all species of grass pollen which will produce positive skin reactions in almost all patients who are clinically sensitive to grass pollen. This phenomenon has usually been demonstrated by intradermal skin testing with use of titration methods which permit sufficient concentration of the grass pollen extract to be used to produce a positive reaction in almost all grass-sensitive patients. Cooke (Ref. 107) compared intradermal skin test reactions to six grasses (orchard, June, timothy, redtop rye, and wheat) in 20 patients with grass season hay fever and noted that with very few exceptions a positive reaction to one was associated with a positive reaction to all. On the other hand, there was no cross-reactivity between extracts of grass pollens, ragweed pollens, and tree pollens. These observations have been repeatedly confirmed. Scheppegrell (Ref. 192) stated:

> As a result of a long series of tests including over 100 varieties of grass pollens, we have been able to determine that all grasses have a similar hay fever reaction. This similarity differs in degree, but in no case have we found a subject sensitive to one of the grass pollens who did not to a more or less extent react to the other grass pollen with which he was tested. The tests were made by the intradermal method.

Thommen (Ref. 42) tested a series of 30 patients known to be clinically sensitive to grass pollen with extracts from the pollens of 81 species of grass representing 50 genera. Tests were made by the intradermal technique. In each instance a positive reaction varying in degree was obtained. On the other hand, in eight normal individuals used as controls the tests were invariably negative.

Frankland (Ref. 135) noted that of 2,666 patients with grass hay fever, all had positive skin tests to extracts of orchard and timothy pollens. Milner and Tees (Ref. 99) studied 338 patients who had hay fever in the grass pollen season and found that 271 reacted to all 12 grass allergens tested.

Skin testing has also provided evidence which suggests that most species of grass pollen contain some antigens which are unique to that species of grass or to a few species but certainly not to all species of grass pollen. This phenomenon has been best demonstrated by skin testing with a fixed and somewhat dilute concentration such as is accomplished with the prick test. Frankland (Ref. 135) noted that while all 2,666 patients reacted to skin tests to both orchard and timothy pollens, some who reacted gave a larger reaction to one, and some to the other. When Frankland tested with Bermuda grass pollen extracts in 152 patients reacting to orchard and timothy extracts, 44 did not give any reaction to it. Milner and Tees (Ref. 99) noted that all of their 338 patients with hay fever clinically attributed to allergy to grass pollen reacted to prick tests to extracts of one of the following pollens: brome grass (*Bromus mollis*), cocksfoot or orchard grass (*Dactylis gomerulata*), dogstail (*Cynsurus cristatus*), false oat (*Arrhenotherum elatius*), fescue (*Festucae elatior*), foxtail (*Alopecurus pretensis*), meadow or June grass (*poa pratensis*), rye grass (*Lolium perenne*), timothy (*Pheleum pratense*), vernal (*Anthoxanthum oderatum*), wild oat (*Avena fatua*), and velvet or Yorkshire fog (*Holcus lanatus*). Two hundred and seventy (81 percent) reacted to prick tests with all 12 extracts. Each grass produced positive prick tests in a slightly different group of patients. The total numbers of positive reactions for each grass were as follows: brome, 327; orchard, 326; dogstail, 327; false oat, 322; fescue, 324; foxtail, 317; June, 322; rye grass, 324; timothy, 320; vernal, 315; wild oat, 320; and yorkshire fog, 319. The data were interpreted as indicating that while many grass hay fever patients are sensitive to an allergen present in all of these grass pollen extracts, some are sensitive to specific allergenic factors which may be present only in extracts of one or a few species of grass pollen. Similar differences were noted by Piness and Miller (Ref. 185).

b. *Passive transfer neutralization tests.* These studies are difficult to interpret. Excellent critical reviews have been published by Wodehouse (Refs. 160 and 179). The method suggests differences between the antigens in Bermuda grass and timothy and between those in June grass and timothy. The method also suggests that there are shared antigens.

c. *Radioallergosorbent tests.* Leiferman and Gleich (Ref. 178) have shown by radioallergosorbent methods that meadow fescue (*Festuca elatior*), June, orchard, and perennial rye (*Lolium perenne*) grass extracts are remarkably similar in terms of their allergenic makeup when they are reacted with a pool of sera from individuals clinically sensitive to northern grasses from the Minnesota area. Timothy was less closely related and possessed a unique antigen. Bermuda grass appeared to be even less closely related.

Bernstein et. al. (Ref. 91) showed close similarity between the antigens in timothy, June, orchard, sweet vernal, and meadow fescue pollen extracts and differences between these antigens and those in Bermuda grass and common

reed (*Phragmites communis*) pollen extracts by radioallergosorbent methods.

d. *Antigenic analysis.* Chromatographic analysis by Marsh and coworkers (Ref. 127) has shown that rye grass contains three distinct protein allergens which have been designated Group 1, (molecular weight 27,000), Group II (molecular weight 11,000) and Group III (molecular weight 11,000). These three allergens are found in varying proportions in various grass pollens. All three groups are found in rye, fescue, orchard and velvet grass pollen extracts. Sweet vernal and timothy pollen extracts contained antigens with cross-reactivity to Groups I, II, and III of rye grass but were not as closely related to rye as were the respective antigens of fescue, orchard and velvet. In particular, there were significant differences in antigenic structure between rye and timothy Group I antigens. Bermuda grass extracts contained no Groups II, II or III antigens and thus differed markedly from the other grass pollen antigens studied. Rye Groups I and II showed incidences of skin sensitivity of 85 percent and 63 percent respectively in 28 individuals sensitive to grass pollen in one study (Ref. 127) and in 90 percent and 67 percent respectively in another (Ref. 186). Lichtenstein, Marsh, and Campbell (Ref. 137) have shown that both Group I and II allergens are highly active by the histamine release test and that by this method there is no cross-reactivity between the two groups, or with Antigen E in ragweed pollen (Ref. 137).

Norman and Lichtenstein (Ref. 191), in a comparative study of the biologic potency of rye Group I antigen relative to that of a crude mixed extract of five grass pollens (30 percent timothy, 30 percent orchard, 20 percent sweet vernal, 10 percent redtop, 10 percent June grass) in 87 patients, found that almost all grass-sensitive patients were highly reactive to rye Group I antigens, and that their sensitivity to rye Group I antigen correlated highly and significantly with their sensitivity to crude grass as measured by quantitative histamine release or skin test assays. Baer et al. (Ref. 184) employed rye Group I antigen content (measured by immunodiffusion against hyperimmune rabbit antiserum) as a method of determining the potency of commercially prepared June, velvet, redtop, rye, fescue, and sweet vernal grass pollen extracts. There was a high correlation between skin reactivity and Group I allergen content. They felt that orchard grass extracts could also be standardized by this method. They had preliminary data which indicated that timothy Group I antigens do not cross-react sufficiently with rye Group I antigens to be standardized by this method.

Timothy grass pollen extracts have been shown to contain unique antigens. Malley and co-workers (Ref. 130) have demonstrated a nondialyzable fraction, antigen B, with a molecular weight of about 10,500 and a dialyzable fraction, antigen D, with a molecular weight of about 5,000. Antigen D has been shown to produce positive skin reactions in timothy-sensitive patients, and can inhibit immunologic reactions in experimental animals. It has been suggested that antigen D has certain properties of a hapten.

Effectiveness for skin test diagnosis. There is considerable evidence indicating that grass pollen extracts are effective for skin test diagnosis of grass pollinosis. This evidence has been derived fraom a number of lines of investigation.

a. *Skin testing.* The studies previously discussed in the section on skin test specificity establish that the patient with hay fever symptoms which have been clinically attributed to allergy to grass pollen usually has been found to have a positive skin test to grass pollen, whereas nonallergic patients usually have been found to have negative skin tests (Refs. 42, 99, 107, 135 and 192). An extract of almost any species of grass pollen will suffice for screening skin test diagnosis provided that enough extract is used. However, extracts of many species must be available for testing because the particular species or multiple species producing the patient's hay fever symptoms often contain more antigens to which the patient is sensitive (Refs 99, 135 and 185) and will therefore produce positive skin tests when tested in lower concentration than will extracts of species which are not responsible for the hay fever symptoms. In practice, most allergists working in the United States use at least one extract of the closely related grass pollen species which include orchard, June, perennial rye, and fescue, plus the less closely related but very abundant timothy, and in the southern states Bermuda and Johnson grasses (Refs. 91, 99, 127, 135, 178, 184 and 185).

b. *Provocation testing.* There is considerable evidence indicating that patients with positive eve, nasal, or bronchial provocation or challenge tests with a particular grass pollen extract usually have hay fever symptoms clinically attributable to that pollen, and positive skin tests to extracts of that pollen, and IgE antibody to that pollen demonstrable by radioallergosorbent tests.

Ahlstedt, Eriksson, Lindgren and Roth (Ref. 93) Studied 24 patients with positive nasal provocation tests with timothy grass pollen, and found that 23 had positive skin tests and 24 had positive radioallergosorbent tests with timothy pollen extracts. There was excellent correlation between the results of timothy pollen nasal provocation tests and the presence of clinical hay fever in the timothy pollen season. Patients with strong reactions to low concentrations of timothy pollen extract by either skin or radioallergosorbent testing invariably had positive nasal provocation tests. Skin tests were negative in six patients who had negative nasal provocation tests, and radioallergosorbent test were negative in four of these. Extracts were obtained from Pharmacia Laboratories.

Pepys, Roth and Carroll (Ref. 100) studied 141 patients suffering from asthma and/or rhinitis. A comparison was made between the result of skin prick test, radioallergosorbent tests (RAST) and nasal provocation tests with grass pollen extracts and a history of hay fever in the grass pollen season:

87 were prick test positive to three concentrations of extracts of sweet vernal, cocksfoot (orchard) meadow fescue, perennial rye, timothy, and meadow (June). With adequate concentration any of the extracts would have sufficed for skin tests, but cocksfoot (orchard) pollen was the most potent. Correlations found were: positive RAST/positive prick test, 98 percent; positive prick test/positive RAST 89 percent; positive RAST/positive nasal test, 75 percent; and the higher the RAST the closer the correlation and the higher the nasal sensitivity; nasal test positive/RAST negative 17 percent; positive history/positive RAST, 91 percent; positive history/positive prick test, 92 percent.

Extracts for prick and nasal tests were made by Beecham Laboratories, England; extracts for RAST tests were made by Pharmacia Laboratories, Sweden.

Stenius, Wide, Seymour, Holford-Strevens and Pepys (Ref. 101) studied 95 patients with varying combinations of hay fever, asthma, and exzema. A comparison was made between the results of skin prick tests with grass pollen extracts, level of specific IgE to grass pollen extract measured by radioallergosorbent tests, nasal provocation tests with grass pollen extracts and a history of hay fever in the grass pollen season. The grass pollen extract tested was "mixed grass pollen extract" obtained from Beecham Laboratories.

Serological measurements of specific IgE to grass pollen showed statistically highly significant correlations with prick tests reactions, the sizes of wheals elicited, nasal tests, and the clinical history. In subjects with negative prick tests, intracutaneous tests gave reactions which were not associated with specific IgE or reactions to nasal tests. . . . The reactions to prick tests identified almost all subjects with specific IgE.

Bryant, Burns, and Lazarus (Ref. 97) studied 153 patient with asthma. A comparison was made between the results of skin prick, bronchial provocation and radioallergosorbent tests with perennial rye pollen extracts, and a history of worsening of the asthma during the spring pollen season. Perennial rye grass pollen extracts were obtained from Hollister-Stier Laboratories. One hundred and four patients had positive bronchial provocation tests; 87 of these had positive and 17 had doubtfully positive skin prick tests. Forty-nine patients had negative bronchial provocation tests; 34 of these had negative, 10 had doubtfully positive and 2 had positive skin prick tests. Of the 107 patients with positive bronchial provocation tests, 98 had positive and only 9 had negative radioallergosorbent tests. Of the 46 patients with negative bronchial provocation tests, 45 had negative and only 1 had positive radioallergosorbent tests. Of 84 patients with positive bronchial provocation tests to both rye and plantain pollens, 57 had a positive and 27 a negative history of worsening in the spring pollen season. Of 69 patients with a negative bronchial provocation test to both rye and plantain pollens, 57 had a negative and 12 a positive history of asthma worsening during the spring pollen season.

Similar correlations between the results of skin, radioallergosorbent and provocation tests with timothy pollen extracts have been reported by Aas and Johansson (Ref. 92) and Berg, Bennich and Johansson (Ref. 96).

c. *Histamine release studies.* There is evidence indicating that patients with clear cut seasonal hay fever from grass pollen and positive skin tests to grass pollen extracts have leukocytes (basophils) which will release histamine upon exposure to grass pollen extracts.

Van Arsdel and Middleton (Ref. 129) Reported seven patients clinically sensitive to grass pollen with leukocyte histamine release by timothy grass pollen extracts.

Lichtenstein, Marsh, and Campbell (Ref. 137) reported that rye Group I and Group II antigens released histamine from the leukocytes of grass-sensitive patients but no from leukocytes of ragweed-sensitive patients.

Norman and Lichtenstein (Ref. 191) studies 87 patients with complaints suggestive of spring hay fever. In general there was good correlation between cell senstivity to release histamine from challenge with either rye Group I or mixed grass extract (timothy 30 percent, orchard 30 percent, sweet vernal 20 percent, redtop 10 percent, June 10 percent) and sympton scores during the grass pollen season.

d. *Passive transfer studies.* Passive transfer studies were reviewed by Wodehouse (Refs. 160 and 179). The studies provide evidence indicating that the patient who is clinically sensitive to grass pollen and has a positive skin test to grass pollen has a factor in his serum (now established to be specific IgE) which will transfer skin reactivity to the skin of a nonallergic patient. Much of the best data showing that grass pollen extracts will not produce skin reactions in the nonallergic patient is contained in these studies.

e. *Radioallergosorbent tests.* These tests provide evidence that patients clincally sensitive to grass pollen, and with positive skin tests to grass pollen, have specific IgE antibody to ragweed pollen in their serum.

The correlations of radioallergosorbent tests with skin tests, with nasal and bronchial provocation tests and with history of grass pollen allergy were discussed above in regard to provocation tests (Refs. 93, 97, 100 and 101).

Leiferman and Gleich (Ref. 178) recruited 18 patients who responded to an advertisement seeking individuals with symptoms of allergic rhinitis in May-June. All patients had positive skin tests to several "norther grass" pollen extracts. The five patients' serum having the greatest reactivity with June grass extract were selected to make the pooled grass pollen serum that was used for the radioallergosorbent tests employed for the grass pollen specificity studies discussed in detail in the section on "Specificity."

Bernstein, Perera, Gallagher, Michael, and Johansson (Ref. 91) screened 500 untreated allergic patients for the presence of specific IgE antibodies to a battery of grass pollen allergens including timothy, June, orchard, sweet vernal, meadow fescue, perennial rye, Bermuda, and common reed. Fifty serum samples showed radioallergosorbent activity toward one or more of the eight grass species. Positive scratch tests were obtained to one or more grassses in each patient with a strongly positive radioallergosorbent test. Differences and similarities between the reactivity and antigens of the various grass species were noted and have been discussed above under "Specificity".

Effectiveness for immunotherapy. There is evidence indicating that aqueous grass pollen extracts are effective for immunotherapy of patients with hay fever and asthma from allergy to grass pollen. This evidence has been derived from a number of lines of investigation.

a. *Reduction in severity of symptoms from grass pollen hay fever and asthma.* Frankland and Augustin (Ref. 183) conducted a controlled study which demonstrated that grass pollen extracts were effective for immunotherapy of grass pollinosis. Patients with seasonal grass pollen hay fever with or without associated seasonal asthma were studied. By random selection, 50 patients were placed in each of 4 comparable extract treatment groups: Pollacine (a mixture of timothy and cocksfoot pollen), purified pollen protein, phenol saline and ultrafiltrate.

The Pollacine group received injections of a mixture of crude extracts of timothy and cocksfoot (orchard) grasses containing 100,000 Noon units per mL by the preseasonal method until a maximum dosage of 20,000 Noon units per injection was obtained. The purified pollen protein group received injections of a pollen-protein concentrate obtained by ultrafiltration of Pollacine which was prepared so that it contained the equivalent of 100,000 Noon units per mL and was given to the same dosage used for the Pollacine group. The phenol saline solution group received phenol saline solution colored slightly yellow with burnt sugar and represented a placebo control group. The ultrafiltrate group received the ultrafiltrate removed when the purified pollen protein was concentrated by ultrafiltration of Pollacine, and represented another control group.

The solutions given to both control groups were made up to contain the equivalent of 100,000 Noon units per mL and were given preseasonally to a maximum dosage of 20,000 Noon units. After the course of treatment was completed, the patients were reviewed, and the results of treatment were recorded in ignorance of the kind of treatment which the patient had received. The patients kept daily record charts of their symptoms and at the end of the trial were asked for their overall impression of the result of treatment. Treatment results were classified as excellent, good, moderate, or poor by appropriate criteria defined before the onset of the study. The results of the different treatments for hay fever and

asthma are shown in Tables 8 and 9 and clearly demonstrate that the two active extracts, Pollacine and purified pollen protein, produced a significantly greater number of excellent and good responses than did the two control solutions, phenol saline solution and ultrafiltrate.

TABLE 8.—Results of Different Treatments of Seasonal Hay-Fever in 198 PATIENTS

Results	Polla-cine	Purified pollen protein	Phenol saline solu-tion	Ultrafil-trate
Excellent	13	13	1	0
Good	27	25	14	18
Moderate	4	6	11	4
Poor	6	5	24	27

TABLE 9.—Results of 4 DIFFERENT TREATMENTS OF SEASONAL POLLEN ASTHMA IN 57 PATIENTS

Results	Polla-cine	Purified pollen protein	Phenol saline solu-tion	Ultrafil-trate
Excellent	15	8	4	3
Good	1	5	0	1
Moderate	0	0	2	1
Poor	1	1	6	9

The Frankland and Augustin study employed an equal-parts mixture of timothy and cocksfoot (orchard) grass pollent extracts, probably for the reasons discussed previously under "Specificity." Timothy and orchard grass are the two most profuse pollen producers in England (Ref. 135). Their pollens contain both cross-reacting and distinct antigens (Refs. 99, 127, 135, 178, and 184). This study therefore presents evidence for the efficacy of immunotherapy with a commonly employed mixture of grass pollen extracts which contains (1) a representative of the closely related grass pollen species which include orchard, June, perennial rye, and fescue, and (2) timothy grass pollen which is less closely related to the other grasses but usually very abundant, and often in the air at the same time as the other grasses.

Frankland and Augustin also compared the results of immunotherapy with (1) untreated equal parts mixture of timothy and orchard pollen extracts (untreated pollen extract) obtained from Parke, Davis and Company, (2) the same extract heated to 98 to 100° C for 4 minutes, (3) the same extract digested with pepsin to remove almost all (greater than 99 percent) of the original skin activity, and (4) the same extract extracted with diethylene glycol (DEG) to remove carbohydrate components (Ref. 134). The DEG extract was fully active by skin test. Patients had grass pollen hay fever or asthma and positive prick tests with timothy and orchard pollen extracts. They were randomly assigned to the four treatment groups. No bias was evident when the four treatment groups were scrutinized for sex, age, and age at onset. A satisfactory high dosage was obtained by most patients regardless of the type of treatment given. Daily charts of symptoms were kept by each patient and reviewed at the end of the season by the physician without knowledge of the kind of specific treatment used. The authors state:

> Among hay fever patients there was little to choose between the results of treatment with crude pollen, heated extracts, or DEG extracts. The proportion of "satisfactory" results obtained in these groups (98, 91, and 91 percent respectively) were all considerably higher than in the group treated with pepsin digested pollen extract (55 percent). A similar pattern emerged from the results of treatment of hay asthma, in that pepsin-digested pollen extract again compared unfavorably with the other three extracts.

These results demonstrate the effectiveness of immunotherapy with an equal-parts mixture of timothy and orchard pollen extract for grass pollen hay fever and asthma. They further indicate that the active principle is relatively heat stable, and resistant to removal by extraction procedures which eliminate carbohydrate. The active principle is destroyed by sufficient protein digestion with pepsin to remove greater than 99 percent of skin reacting activity.

Munro-Ashman, McEwen, and Feinberg (Ref. 195) studied clinical and blocking antibody responses of grass hay fever patients who had not received previous grass pollen immunotherapy. Patients were randomly placed in two groups and treated in a double-blind manner with either alum-precipitated pyridine-extracted mixture of orchard, timothy, perennial rye, Yorkshire fog (velvet grass), and meadow fescue pollens or with a placebo. Treatment consisted of 9 weekly doses to a total dosage of 4,000 PNU. Clinical response was better in the treated group; 82 percent of the treated patients had a good or very good response, whereas only 40 percent of placebo-treated patients has such a response. Blocking antibody levels rose briskly in all Allpyral™ treated patients (at least 25 fold), but did not increase in the placebo treated patients.

Starr and Weinstock (Ref. 196) studied patients with grass pollen hay fever who had positive skin tests to timothy pollen extract. Forty-two received weekly injections of alum-precipitated pyridine extracted timothy pollen extracts prepared in Great Britain. Of these, 26 received a total of 4,880 PNU, 10 received a total of 9,570 PNU, and 6 were given a total of 20,650 PNU. Ten control patients received weekly placebo injections. Thirty-three (79 percent) of the 42 patients treated with the timothy extract showed a substantial improvement over the preceding season, whereas only one (10 percent) of the 10 control subjects improved at all. The assessment was made by a physician who did not know which treatment the patient had received. Blocking antibody levels as measured by histamine release inhibition were much higher in timothy pollen extract treated patients than in controls, and there was a significant correlation between the quantity of blocking antibody and the severity of a patient's symptoms. The study suffers from failure to randomize and match treatment groups.

b. *Increase in specific IgG blocking antibody.* Zavazal and Stajner (Ref. 190) have shown an increase in IgG antibodies to timothy pollen extract following 4 months of immunotherapy with aqueous timothy pollen extracts. Extracts were prepared in Czechoslovakia; a total of 84,000 PNU of antigen was given to each of the 60 patients. Patients with higher levels of IgG antibody tended to have less severe hay fever symptoms than did those with lower levels. There were no untreated control subjects in their study.

Fagerberg, Nilzen, and Wiholm (Ref. 189) studied 19 patients who had both positive skin and provocation (either nasal or bronchial) tests with aqueous timothy pollen extracts made by Dome Laboratories (probably in Europe) or Vitrum Laboratories, Sweden. All patients received immunotherapy with alum-precipitated, pyridine extracted timothy extracts every week until a maximum dose, usually 0.4 to 1.0 ml of 10,000 PNU/mL, was achieved and maintained until 50 treatment courses had been given. Provocation tests carried out before and after treatment revealed increased tolerance to timothy extract in 16 of the 19 patients. However, the tolerance of paired untreated controls was not measured. Serum was taken from six of the patients before and after immunotherapy and studied for reagin content by passive skin transfer and for specific blocking antibody by passive transfer neutralization techniques. Increase in blocking antibody was demonstrated in all serums; reagin titers remained unchanged.

Weinstock and Starr (Ref. 194) studied blocking antibody levels of patients with

grass pollen hay fever who had not previously received injection treatment for their hay fever. Nine received aqueous timothy pollen extracts (made by Beecham Research Laboratories, Great Britain) 44 injections 3 times/week to a total of 69,000 PNU; 10 received alum-precipitated pyridine-extracted timothy grass pollen extracts (Dome Laboratories, Great Britain, Allpyral™) 9 weekly injections to a total of 4,800 PNU; and 9 controls received antihistamines only. Those patients receiving either aqueous or alum-precipitated extracts developed large quantities of blocking antibody to timothy grass pollen, whereas the controls did not.

Malley and Perlman (Ref. 128) studied blocking antibody responses of patients with a history of grass pollen hay fever who had a strong skin reaction to timothy pollen extract given intradermally at a concentration of 10^{-6} grams (g) of protein per mL. Twelve patients were given aqueous timothy pollen extract and reached a dose of 160 micrograms of protein nitrogen without significant immediate or delayed reactions or any systemic reactions. Ten of the 12 had a rise in blocking antibody titer. Twenty-three patients treated with timothy antigen D and 19 treated with timothy pollen extract in alginate showed insignificant or no rise in blocking antibody. The extracts were prepared by the authors.

Marsh, Lichtenstein, and Norman (Ref. 187) studied blocking antibody responses of nonallergic humans to Group I allergen prepared from perennial rye grass pollen and to its allergoid prepared by incubating the allergen with dilute formaldehyde. Nine of nine subjects (three native allergen, six allergoid) developed blocking IgG antibody. In addition, six developed immediate skin reactivity (3/3 native allergen, 3/6 allergoid), which was passively transferred in 3/3. IgE immunosorbent blocked passive transfer in 2/2. Leukocytes from six subjects (three native allergen and three allergoid) released histamine after exposure to the immunizing allergen. The induction of immediate skin reactivity and leukocyte sensitivity, and the passive transfer of skin sensitivity by IgE were interpreted as induction of IgE mediated immediate hypersensitivity to Group I rye grass pollen allergen and allergoid in nonallergic man. However, these sensitized individuals had no symptoms of pollinosis during the grass pollen season, and the one subject who was tested had a negative conjunctival challenge test. The allergens employed were made by the authors.

Specific grass pollens—a. *Festuceae tribe*—(1) *Bromus or brome grasses.* The bromes are annual or perennial grasses which are found in Europe and in much of the United States, particularly in the western United States. Some are important forage grasses in the mountainous regions of the western United States. Brome or soft chess (*B. mollis*) is the prototype species. Other species include smooth or Hungarian brome (*B. inermis*), California brome (*B. carinatus*), soft chess or brome chess, cheat, or rye-brome (*B. secalinus*), and ripgut grass (*B. rigidus*). The brome grasses usually pollinate in June or July. Most shed relatively little pollen, and they are not regarded as major causes of hay fever, though they may occasionally be contributing factors (Ref. 43, 45, and 152).

Effectiveness for skin test diagnosis. There is evidence from controlled studies which indicates that brome grass pollen extracts are effective for skin test diagnosis of brome pollinosis (Refs. 42 and 99). This evidence was reviewed above in the general discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with brome grass pollen extracts will reduce symptoms of brome grass pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Extracts of orchard and timothy grass pollens which are antigenically related to brome grass have been shown to be effective for imunotherapy of grass pollinosis as reviewed above in the discussion of the grass family.

Recommendations. The Panel recommends that *Bromus* species pollen extracts be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

(2) *Festuca or fescue grasses.* The fescue grasses are annual or perennial grasses which are found all over the Northern Hemisphere and which are used as both forage and lawn grasses all over the cooler parts of the United States. Meadow fescue (*F. elatior*) is the prototype species. Other species include red fescue (*F. rubra*) and sheep fescue (*F. ovina*). The fescues flower in June and July and are moderately important causes of hay fever (Refs. 42, 43, 45, 64, and 152).

Effectiveness for skin test diagnosis. There is evidence from controlled studies which indicates that fescue grass pollen extracts are effective for skin test diagnosis of fescue pollinosis (Refs. 42, 91, 99, 100, 178, and 184). This evidence was reviewed above in the discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with fescue grass pollen extracts is effective. Extracts of orchard and timothy grass pollens, which are antigenically related to fescue grass, have been shown to be effective for immunotherapy of grass pollinosis as reviewed above in the discussion of the grass family.

Recommendations. The Panel recommends that extracts of *Festuca* species pollens be placed in Catetory I for skin test diagnosis and Category IIIA for immunotherapy.

(3) *Poa or bluegrasses.* The bluegrasses are perennial, rarely annual, grasses which are widely distributed in all temperate regions where they grow wild and are extensively cultivated for lawn and pasture. Orchard grass or cocksfoot (*Dactylis glomerulata*) is the prototype species and one of the most important procedures of pollen causing hay fever. Other species include June grass (*Poa pratensis*), Canada bluegrass (*P. compress*), annual bluegrass (*P. annua*) and rough bluegrass (*P. trivialis*). Orchard and June grass flower in May and June and produce large amounts of highly allergenic pollen which is a very important cause of spring hay fever. Annual bluegrass pollinates as early as April but liberates little pollen and therefore is of little importance as a cause of hay fever (Refs. 42 through 45, 64, and 151).

Effectiveness for skin test diagnosis. There is abundant evidence from controlled studies which indicates that orchard grass pollen extracts are effective for skin test diagnosis of orchard grass pollinosis (Refs. 42, 91, 99, 100, 107, 127, 135, 137, 178 and 191). This evidence was reviewed above in the general discussion of the grass family. In the same section, there is also evidence from controlled studies which indicates that June grass (Refs. 42, 91, 99, 100, 107, 178, 184, and 191), annual bluegrass (Ref. 42), and rough bluegrass (Ref. 42) pollen extracts are effective for this purpose.

Effectiveness for immunotherapy. Mixtures of equal parts of orchard and timothy grass pollen extracts have been shown by controlled studies to be effective for immunotherapy of grass pollinosis. The studies demonstrating this have been reviewed in the general discussion of the grass family. The Panel found no controlled studies indicating that immunotherapy with bluegrass pollen extracts other than orchard pollen extract are effective for this purpose, but presumes that they would

be in view of their close antigenic similarity ot orchard grass pollen.

Recommendations. The reported results of skin testing with orchard and June grass pollen extracts indicate that they are effective for this purpose. The report results of immunotherapy with orchard grass pollen extract indicate that it is effective for immunotherapy but there is only circumstantial evidence indicating that *Poa* grass pollen extracts are effective for immunotherapy. The Panen recommends that extract of orchard grass pollen be placed in Category I for both skin test diagnosis and immunotherapy and that extracts of *Poa* grass pollens be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

b. *Hordeae tribe*—(1) *Agropyron or wheatgrasses.* The wheatgrasses are perennials which are found in all temperate regions. Quackgrass or couchgrass (*A. repens*) is naturalized from Europe and is found in fields and waste places throughout North America. It flowers from July to September and is a contributing factor in hay fever. Western wheatgrass (*A. smithii*) is found over much of the western United States and Canada, flowers from July to September and is an important contributory cause of hay fever. Wheat (*Triticum aestivum*, L, *T. vulgare*, Vill or *T. sativum* Lam.) is perhaps the commonest cereal grass in cultivation in the world, but it is a negligible factor as a cause of hay fever because it is self pollinating (Refs. 43, 64, and 151).

Effectiveness for skin test diagnosis. There is evidence from controlled studies which indicates that wheatgrass extracts are effective for diagnosis of wheatgrass pollinosis (Refs. 42 and 107). This evidence was reviewed above in the discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with wheatgrass pollen extracts will reduce symptoms of wheatgrass pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Extracts of orchard and timothy grass pollens, which are antigenically related to wheatgrass, have been shown to be effective for immunotherapy of grass pollinosis as reviewed in the discussion of the grass family.

Recommendations. The Panel recommends that extracts of *Agropyron* and *Triticum* species pollens be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

(2) *Hordeum or barley.* The barleys are widely distributed in both hemispheres. The cultivated barley is generally thought to be of no importance in hay fever because it is self pollinating and sheds little or no pollen. Foxtail barley (*H. jubatum*) and mouse barley (*H. murinum*) grow wild in the United States particularly in the western States and have been thought to be possible contributing causes of hay fever (Refs. 42 and 43).

Effectiveness for skin test diagnosis. There is evidence from one controlled study which indicates that barley extracts are effective for diagnosis of grass pollinosis (Ref. 42). This evidence was reviewed above in the discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with barley pollen extracts will reduce symptoms of barley pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Extracts of orchard and timothy grass pollens which are antigenically related to barley have been shown to be effective for immunotherapy of grass pollinosis as reviewed in the discussion of the grass family.

Recommendations. The Panel recommends that extracts of *Hordium* species pollen extracts be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

(3) *Lolium or ryegrass.* Perennial ryegrass (*L. perenne*) is the prototype species. A native of the Old World, it has become naturalized over much of North America. It pollinates in July and August and sheds large amounts of pollen which makes it an important cause of hay fever especially on the Pacific coast. Other species include Italian ryegrass (*L. multiflorum*), darnel (*L. tementulum*), which are also important causes of hay fever in some regions. Rye (*Secale cereale*) is cultivated in Europe and America and sheds large amounts of pollen in May and June which causes some hay fever. However, the large size of rye's pollen grains greatly restricts its effective range (Refs. 42 through 45, 64 and 151).

Effectiveness for skin test diagnosis. This is evidence from controlled studies which indicates that ryegrass extracts are effective for diagnosis of ryegrass pollinosis (Refs. 42, 91, 97, 99, 100, 107, 127, 137, 178, and 185). This evidence was reviewed above in the general discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies which indicate that immunotherapy with ryegrass pollen extracts will reduce symptoms of ryegrass pollinosis better than placebo, or will induce changes in anti-ryegrass pollen IgG or IgE antibodies. Extracts of orchard and timothy grass pollens which are antigenically related to ryegrass have been shown to be effective for immunotherapy of grass pollinosis as reviewed in the discussion of the grass family.

Recommendations. The Panel recommends that extracts of *Lolium* species pollens be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

c. *Aveneae tribe. Avena* or oats are annual or perennial grasses which are widely distributed in the temperate regions of the Old World and America. Velvet grass or Yorkshire fog (*Holcus lanatus*) is the prototype species. It flowers from June to August and is considered to be an important cause of hay fever in England and a contributory cause in California, Oregon and Washington. Wild oat (*A. fatua*) is found in both Europe and the United States and is abundant on the Pacific coast where it is felt to be an important cause of hay fever when it blooms between July and September. Slender wild oat (*A. barbata*) is common in the Pacific coast states and Arizona where it is regarded as a contributory cause of hay fever. The cultivated oat (*A. sativa*) is cultivated in most temperate regions, but is not a factor in hay fever because it is usually self-pollinating. Western June grass (*Koeleria cristata*) is found throughout much of the United States, Canada, Mexico, and Europe and has been thought to be an important cause of hay fever in the western United States (Refs. 42 through 45, 64 and 151).

Effectiveness for skin test diagnosis. There is evidence from controlled studies which indicates that various oat tribe extracts are effective for diagnosis of oat tribe pollinosis (velvet grass Refs. 99, 127, and 184; wild oat Refs. 42 and 99; slender wild oat Ref. 42; cultivated oat Ref. 42). This evidence was reviewed above in the discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies which indicate that immunotherapy with oat tribe pollen extracts will reduce symptoms of oat tribe pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Extracts of orchard and timothy grass pollen which are antigenically related to oat have been shown to be effective for immunotherapy of grass pollinosis as reviewed above in the discussion of the grass family.

Recommendations. The Panel recommends that oat pollen extracts be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

d. *Agrostideae tribe*—(1) *Phleum pratense. Phleum pratense* or timothy is a perennial grass which is commonly cultivated in Europe and America. It is the most important meadow grass in the cooler regions of the United States and is also found growing wild. It flowers during June and July and sheds enormous quantities of pollen which is known to cause hay fever (Refs. 42 through 45, 64 and 151).

Effectiveness for skin test diagnosis. There is evidence from controlled studies which indicates that timothy pollen extracts are effective for diagnosis of timothy pollinosis (Refs. 42, 91, 93, 99, 100, 107, 127, 129, 130, 135, 137, 160, 178, 179, 184, and 191). This evidence was reviewed above in the discussion of the grass family.

Effectiveness for immunotherapy. Mixtures of equal parts of timothy and orchard grass pollen extracts have been shown by controlled studies to be effective for immunotherapy of grass pollinosis as reviewed above in the discussion of the grass family.

Recommendations. The Panel recommends that extract of *Phleum pratense* pollen be placed in Category I for both skin test diagnosis and immunotherapy.

(2) *Agrostis alba or redtop, whitetop, or creeping bent grass.* Redtop is a perennial grass which is cultivated as a meadow and pasture grass in Europe and North America. It flowers from June to July at about the same time as timothy, and sheds very large quantities of pollen which is believed together with that of timothy to cause most of the hay fever which occurs in the second half of the grass hay fever season in temperate regions (Refs. 42 through 45, 64, and 151).

Effectiveness for skin test diagnosis. There is evidence from controlled studies which indicates that redtop grass pollen extracts are effective for diagnosis of redtop grass pollinosis (Refs. 42, 107, 184, and 191) which is reviewed above in the discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with redtop grass pollen extracts will reduce symptoms of redtop grass pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Extracts of orchard and timothy grass pollens which are antigenically related to redtop grass have been shown to be effective for immunotherapy of grass pollinosis as reviewed above in the discussion of the grass family.

Recommendations. The Panel recommends that extracts of *Agrostis* species pollens be placed in Category I for skin test diagnosis and Category IIIA for Immunotherapy.

e. *Chlorideae tribe*—(1) *Cynodon dactylon or Bermuda grass.* Bermuda grass is a perennial grass which is common in the southern United States from coast to coast and in dry ground in the warm parts of both hemispheres. It is abundant, widely distributed. and produces copious buoyant pollen throughout the growing season which may extend over 11 months in warner climates. It is a very important cause of hay fever (Refs. 42 through 45, 64 and 151).

Effectiveness for skin test diagnosis. There is evidence from controlled studies which indicates that Bermuda grass pollen extracts are effective for diagnosis of Bermuda grass pollinosis (Refs. 42, 91, 127, 135, 160, 178, 179, and 185) which is reviewed above in this discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies which indicate that immunotherapy with Bermuda grass pollen extracts will reduce symptons of Bermuda grass pollinosis better that placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. The Panel recommends that extract of *Cynodon dactylon* pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

(2) *Bouteloua or grama grass.* The gramas are perennial and sometimes annual grasses found in North America. These were important constituents of the native pastures of the northern prairie region between the Mississippi River and the Continental Divide, and between Canada and Mexico. The gramas are modest pollen shedders and may be of importance as causes of hay fever in some prairie States. They flower from July to September (Refs. 43 and 45).

Effectiveness for skin test diagnosis. The Panel did not find evidence from controlled studies which indicated that grama grass pollen extracts are effective for diagnosis of grama pollinosis.

Effectiveness for immunotherapy. The Panel found no published descriptions of immunotherapy with grama pollen extracts.

Recommendations. The Panel recommends that extracts of *Bouteloua* species pollens be placed in Category IIIA for both skin test diagnosis and immunotherapy.

f. *Phalarideae tribe*— (1) *Anthoxanthum odoratum or sweet vernal grass.* Sweet vernal grass is a perennial commonly found in Europe, Asia and North America. It is a common field, meadow, and roadside grass in the eastern parts of the United States and Canada and on the Pacific coast. It blooms from the first week in May until the end of June and is one of the most important hay fever producing grasses (Refs. 42 through 45, 64, and 151).

Effectiveness for skin test diagnosis. There is evidence from controlled studies which indicates that sweet vernal grass pollen extracts are effective for diagnosis of sweet vernal grass pollinosis (Refs. 42, 91, 99, 100, 127, 184, and 191) which is reviewed above in the discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies which indicate that immunotherapy with sweet vernal grass pollen extracts will reduce symptoms of sweet vernal grass pollinosis better than placebo, or will induce changes in specific pollen IgG or IgE antibodies. Extracts of orchard and timothy grass pollens which are antigenically related to sweet vernal grass have been shown to be effective for immunotherapy of grass pollinosis as reviewed in the discussion of the grass family.

Recommendations. The Panel recommends that extract of *Anthoxanthum oderatum* pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

(2) *Phalaris or canary grass.* Mediterranean canary grass (*P. minor*) is an annual introduced from Europe and found sparingly in Louisiana and Texas, and more abundantly in California, where it blooms in August and has been suspected of causing hay fever. Reed canary grass (*P. arundinacea*) is cultivated between Northern California and Washington State for hay and pasture. Canary grass (*P. canariensis*) is found in small amounts throughout most of the United States but is seldom abundant. It is used as a source of canary seed. None of these species of *Phalaris* are considered to be important causes of hay fever (Refs. 42 through 45 and 64).

Effectiveness for skin test diagnosis. There is evidence from one controlled study which indicates that canary grass pollen extracts are effective for diagnosis of canary grass pollinosis (Ref. 42). This evidence has been reviewed in the general discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies which indicate that immunotherapy with canary grass pollen extracts will reduce symptoms of canary grass pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Extracts of orchard and timothy grass pollens which are

antigenically related to canary grass have been shown to be effective for immunotherapy of grass pollinosis as reviewed in the discussion of the grass family.

Recommendations. The Panel recommends that extracts of *Phalaris* species pollens be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

g. *Paniceae tribe*— (1) *Digitaria sanguinalis or crab grass.* Crab grass is a native of Europe, but is now a troublesome weed throughout the United States. Despite the great abundance of the plants, it does not produce enough pollen to be of importance as a cause of hay fever (Refs. 42 through 45 and 64).

Effectiveness for skin test diagnosis. There is evidence from one controlled study which indicates that crab grass pollen extracts are effective for diagnosis of crab grass pollinosis (Ref. 42) as reviewed in the discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies which indicate that immunotherapy with crab grass pollen extracts will reduce symptoms of crab grass pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Extracts of grass pollen antigenically related to crab grass, orchard and timothy have been shown to be effective for immunotherapy of grass pollinosis as reviewed in the discusssion of the grass family.

Recommendations. The Panel recommends that extract of *Digitaria sanguinalis* pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

(2) *Paspalum or dallis grass.* Dallis grass is a native of South America, recently introduced in the United States and cultivated as a pasture grass in the Southeastern States. It may be found in meadows from New Jersey to Florida, and west to Texas and Arkansas. It flowers from early spring to late fall and is believed to be a contributory cause of hay fever (Refs. 42, 43, 64, and 151).

Effectiveness for skin test diagnosis. There is evidence from one controlled study which indicates that dallis grass pollen extracts are effective for diagnosis of dallis grass pollinosis (Ref. 42) as reviewed in the discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies which indicate that immunotherapy with dallis grass pollen extracts will reduce symptoms of dallis grass pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Extracts of grass pollens antigenically related to dallis grass, orchard and timothy, have been shown to be effective for immunotherapy of grass pollinosis as reviewed in the discussion of the grass family.

Recommendations. The Panel recommends that extract of *Paspalum* grass pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

h. *Andropogoneae tribe*—(1). *Sorghum halepense Pres. (Holcus halepensis L., Andropogon halepensis Brot.) or Johnson grass.* Johnson grass is a perennial introduced into the United States from the Mediterranean area as a forage plant for arid regions because it has great drought resisting qualities. It has spread throughout most of the warmer parts of the United States and extends from New Jersey south to Florida and west to southern California. It flowers from July to September and is believed to be a cause of hay fever (Refs. 42 through 45, 64, and 151).

Effectiveness for skin test diagnosis. There is evidence from one controlled study which indicates that Johnson grass pollen extracts are effective for diagnosis of Johnson grass pollinosis (Ref. 42) which is reviewed in the discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies which indicate that immunotherapy with Johnson grass pollen extracts will reduce symptoms of Johnson grass pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Extracts of grass pollens antigenically related to Johnson grass, orchard and timothy, have been shown to be effective for immunotherapy of grass pollinosis as reviewed in the discussion of the grass family.

Recommendations. The Panel recommends that extract of *Sorghum halepense* pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

(2) *Sorghum vulgare or sorghum.* Sorghum is an annual which has been cultivated since prehistoric times for forage and for its juice which is made into syrup. A variety known as Sudan grass (*Var. sudanensis*) is extensively grown for hay and pasture. Sorghums are widely cultivated in America (Ref. 43).

Effectiveness for skin test diagnosis. The Panel found no evidence from controlled studies which indicates that sorghum pollen extracts are effective for diagnosis of sorghum grass pollinosis. One publication indicates or implies that sorghum pollen extracts are effective for skin test diagnosis of sorghum pollinosis (Ref. 43).

Effectiveness for immunotherapy. The Panel found no report of immunotherapy with sorghum.

Recommendations. The Panel recommends that extract of *sorghum Vulgare* pollen be placed in Category IIIA for both skin test diagnosis and immunotherapy.

i. *Tripsaceae tribe. Zea Mays* or maize, Indian corn, or corn is cultivated throughout the world, and over much of the United States. It produces pollen which will produce hay fever symptoms in grass pollen sensitive patients, but which is so large that it is not spread to sufficient degree by the wind to make it of importance other than to those in direct contact with the pollinating plants (Refs. 42, 43, and 64).

Effectiveness for skin test diagnosis. There is evidence from one study which indicates that maize pollen extracts are effective for diagnosis of maize pollinosis (Ref. 42) as reviewed in the discussion of the grass family.

Effectiveness for immunotherapy. The Panel found no controlled studies which indicate that immunotherapy with maize pollen extracts will reduce symptoms of maize pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Extracts of grass pollen antigenically related to maize, orchard and timothy, have been shown to be effective for immunotherapy of grass pollinosis as reviewed in the discussion of the grass family.

Recommendations. The Panel recommends that extract of *Zea* species pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

9. *Cyperaceae family—Carex or sedge.* This is the prototype *Cyperaceae* family pollen. The sedges are widely distributed in temperate zones particularly in bogs and other moist places (Ref. 43). They flower in April and May and produce much pollen, which appears to be of little if any importance in hay fever, though occasionally recorded as a possible cause (Refs. 43 and 44).

The Panel found no study of the antigens and allergens in sedge pollen or of their relationships and cross-reactions with antigens and allergens in other species of pollens.

Effectiveness for skin test diagnosis. No controlled studies were found indicating that sedge pollen extracts are effective for skin test diagnosis of patients with sedge pollinosis.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with sedge pollen extracts will reduce symptoms of sedge pollinosis better

than placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. The status of sedge pollen as a cause of pollinosis is unclear at this date. Sedge produces abundant airborne pollen. Sedge pollen extract may be of use in diagnosis and immunotherapy for the occasional patient suspected of having sedge pollinosis. The Panel recommends that extracts of *Carex* and other *Cyperaceae* pollen be placed in Category IIIA for both skin test diagnosis and immunotherapy.

10 *Juncaceae family—Luzula compestis* (syn. *Juncoides campestis*) or wood rush is the prototype *Juncaceae* family pollen. It is common in woods throughout most of North America, and also in Europe and Asia. It produces pollen early in the spring. Though the pollen is wind-borne, it is shed very sparingly, is rarely caught on pollen slides, and is not known to cause hay fever (Refs. 43 and 44).

Effectiveness. The Panel has found no controlled studies indicating that wood rush pollen extracts are effective for skin test diagnosis or for immunotherapy of patients with wood rush pollinosis.

Recommendations. The Panel recommends that *Luzula compestris* and other *Juncaceae* pollen extracts be placed in Category IIIA for both skin test diagnosis and immunotherapy.

11. *Typhaceae family—Typha* or cattail is the prototype *Typhaceae* family pollen. *T. latifolia* (broad-leaved cattail) and *T. agustifolia* (narrow-leaved cattail) are common throughout much of North America except in the extreme north (Ref. 43). Both species shed enormous quantities of pollen which may be picked up on pollen slides miles from where the plants are growing, but which only occasionally causes hay fever (Refs. 43, 44, and 64). They pollinate in June (Refs. 64). The Panel found no study of the antigens and allergens in cattail pollen or of their relationships and cross-reactions with antigens and allergens in other species of pollens.

Effectiveness for skin test diagnosis. The Panel found no controlled studies indicating that cattail pollen extracts are effective for skin test diagnosis of patients with cattail pollinosis.

Vaughan has reported "one farmer boy near whose home there was a marsh with much cattail, who had hay fever at the time of cattail pollination. He gave positive skin reactions and was promptly relieved by coseasonal cattail pollen hyposensitization" (Ref. 64).

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with cattail pollen extracts will reduce symptoms of cattail pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. The status of cattail pollen as a cause of pollinosis is unclear at this date. Cattail produces abundant airborne pollen. Cattail pollen extract may be of use in diagnosis and immunotherapy for the occassional patient suspected of having cattail pollinosis. The Panel recommends that extracts of *Typhaceae* species pollens be placed in Category IIIA for both skin test diagnosis and immunotherapy.

12. *Coniferae family*—a. *Cupressineae,* the junipers and their allies.

(1) *Juniperus. J. sabinoides (J. mexicana,* mountain cedar, Mexican cedar, rock cedar) is the prototype pollen. This species is particularly abundent in central Texas and is also found in Arizona and New Mexico. It pollinates profusely between December and early March and causes severe hay fever and asthma. *J. virginiana* (common red cedar or juniper) is found throughout eastern United States and Canada and pollinates in March and April. *J. bermudiana* (Bermuda cedar) is found in Bermuda and pollinates in March and April. *J. Pinchotii* (red-berried juniper) is found in Texas and Arizona and pollinates in the period between late September and late November. All of these plants shed copious amounts of airborne pollen which may cause hay fever (Refs. 42 through 45, 64, 113, and 151). The pollen of mountain cedar cross reacts with that of other junipers so that a patient sensitive to the one will usually react to others (Refs. 43, 111, and 172). Patients with positive skin tests to mountain cedar pollen usually have positive skin tests to red cedar (Refs. 111 and 114), red-berried juniper (Ref. 172), western red cedar or *Thuja plicata* (Ref. 114), American aroborvitae, or *Thuja occidentalis* Ref. 114), western juniper or *J. occidentalis* (Ref. 114), Port Orford cypress of *Chamaecyparis Lawsoniana* (Refs. 112 and 114), Moneterey cypress or *Cupressus macrocarpa* (Ref. 114), Arizona cypress or *Cupressus arizonica* (Ref. 114), Pfitzer juniper or *Juniperus chinensis* (Ref. 114), and incense cedar or *Libocedurus decurrens* (Ref. 114). Studies to clearly demonstrate antigenic differences as well as similarities between these antigens were not found in the literature cited.

Effectiveness for skin test diagnosis. Kahan and Grothaus (Ref. 111) described 15 patients with mountain cedar pollen hay fever who had positive skin tests to mountain cedar pollen extracts. No skin tests in nonallergic patients were described. No eye, nose, or bronchial challenge, passive transfer, radioallergosorbent, or leukocyte histamine release tests were reported. The source of materials and manufacturing methods for the extracts were not given.

Black (Ref. 112) described 40 patients with hay fever during the mountain cedar season. Thirty-nine had positive skin reactions to mountain cedar pollen extract; 1 had a negative reaction. No skin tests in nonallergic patients were described.

Pence, Mitchell, Greely, Updegraff, and Selfridge (Ref. 108) reported 40 patients with a history of seasonal hay fever and/or asthma during the mountain cedar pollen season who had positive skin reactions to intradermal tests with aqueous extracts of mountain cedar pollen at 1:100,000 w/v concentration. Radioallergosorbent tests were positive in 37 of 37. Extracts were obtained from Greer Laboratories. No skin tests in nonallergic controls were described.

Effectiveness for immunotherapy. Mountain cedar pollen does not have a widespread distribution, but has been recognized to be an important cause of hay fever, chiefly during the winter months around San Antonio and other areas of Texas. Furthermore, during the season, no other pollen is in the air in significant amounts and this phenomenon affords an opportunity to study clincial response without interference from other pollens.

Pence, Mitchell, Greely, Updegraff, and Selfridge (Ref. 108) in a double-blind controlled study demonstrated the effectiveness of mountain cedar pollen extract for immunotherapy of mountain cedar pollinosis. Patients were selected on the basis of history of seasonal hay fever or asthma during the months of November through March, strongly positive skin reactions to mountain cedar pollen extract, and not currently receiving immunotherapy. Thirty-two patients completed the double-blind study which consisted of only one season of treatment. Seventeen patients received relatively high doses of mountain cedar extract and 15 were controls. The patients were assigned to the two groups in random fashion. The groups were very similar in skin reactivity, age, sex, radioallergosorbent test titers, and total serum IgE. Patients treated with specific injection therapy were found to have significantly fewer symptoms than those receiving placebo injections. Specific serum IgE anti-mountain cedar pollen antibodies decreased during the mountain cedar pollen season in the treated group and increased in the placebo group.

Recommendations. Mountain cedar pollen extract has been shown to be effective for both skin test diagnosis and immunotherapy of mountain cedar pollinosis. The Panel found only circumstantial evidence indicating that the other juniper pollen extracts are effective. The Panel recommends that mountain cedar pollen extracts be placed in Category I for both skin test diagnosis and immunotherapy and extracts of other juniper pollens be placed in Category IIIA for both skin test diagnosis and immunotherapy.

(2) *Chamaecyparis* or cypress. *C. Lawsoniana* (Port Orford cedar, Port Orford cypress, Lawson cypress) is the prototype species. The natural habitat of this tree is the moist hillsides and canyons of southern Oregon and Northern California. It has been cultivated in warm moist regions in many parts of the United States. It pollinates in May and sheds large amounts of pollen which may cause hay fever (refs. 43, 44, 64 and 112). Patients with positive skin tests to Port Orford cedar usually also have positive skin tests to mountain cedar or *Juniperus sabinoides,* western red cedar or *Thuja plicata,* American arborvitae or *Thuja occidentalis,* western juniper or *J. occidentalis,* Monterey cypress or *Cupressus macrocarpa,* Arizona cypress or *Cupressus arizonica,* Pfitzer juniper or *Juniperus chinensis,* and incense cedar or *Libocedurus decurrens* (Refs. 112 and 114). Evidence to clearly demonstrate antigenic differences or similarities between these antigens was not found in the studies cited.

Effectiveness for skin test diagnosis. The Panel found no report of the diagnostic use of Port Orford cedar pollen extracts in patients with Port Orford cedar pollinosis.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with Port Orford cedar pollen extracts will reduce symptoms of Port Orford cedar pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Black (Ref. 112) in an uncontrolled study has reported that patients with mountain cedar pollinosis have essentially equal skin reactions to both mountain cedar and Port Orford cedar pollen extracts and that both extracts were equally effective for immunotherapy of mountain cedar pollinosis.

Recommendations. The Panel recommends that extracts of *Chamaecyparis* species pollen be placed in Category IIIA for both skin test diagnosis and immunotherapy.

(3) *Cupressus* or *cypress.* Cypress is found all over the world and particularly in the western United States, Mexico, Europe, Mediterranean area and China. Various species are recognized including *C. sempervirens* (Italian or Mediterranean cypress), *C. arizonica* (Arizona cypress), *C. lusitanica* (Mexican or Portuguese cypress), *C. macrocarpa* (Monterey cypress), and *C. torulosa* (Indian incense cedar). These plants shed large quantities of airborne pollen in winter and early spring which may cause hay fever and/or asthma (Refs. 43 through 45, 140 and 171). Patients with positive skin tests to Arizona cypress usually also have positive skin tests to Monterey cypress, mountain cedar or *Juniperus sabinoides,* western red cedar or *Thuja plicata,* American arborvitae or *Thuja occidentalis,* western juniper or *J. occidentalis,* Pftizer juniper or *Juniperus chinensis,* and incense cedar or *Libocedrus decurrens* (Ref. 114). Evidence to clearly demonstrate antigenic differences or similarities between these antigens was not found in the study cited.

Effectiveness for skin test diagnosis. Tas (Ref. 140) reported four patients with hay fever and/or asthma in mid-February to mid-March in Palestine when exposed to the pollen of *C. sempervirens* or Mediterranean cypress. All had positive skin tests to extracts of the pollen. No skin tests with these extracts were reported in nonallergic controls. The extracts were obtained from a British manufacturer.

Ordman (Ref. 171) reported 13 patients with hay fever during the cypress pollen season between June and October in South Africa. All had positive skin tests to cypress pollen extracts. Negative skin tests were produced by these extracts in "large numbers" of control patients who were not sensitive to cypress pollen. The eye challenge test with cypress pollen extract was positive in the 1 patient tested. At least some of the extracts were prepared in South Africa.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with cypress pollen extracts will reduce symptoms of cypress pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Tas (Ref. 140) and Ordman (Ref. 171) reported that immunotherapy with cypress pollen extracts reduced symptoms of pollinosis in cypress pollinosis patients but did not supply data from controlled studies.

Recommendations. The Panel recommends that extracts of *Cupressus* species pollens be placed in Category I for skin test diagnosis and in Category IIIA for immunotherapy.

(4) *Cryptomeria japonica. C. japonica* or Japanese cedar is the most common conifer in Japan and lives only in Japan. It sheds large amounts of airborne pollen between February and April which may cause hay fever (Ref. 173). Yoo, Spitz, and McGerity (Ref. 114) have reported that 4 of 7 patients with positive skin reactions to mountain cedar extract had positive skin reactions to Japanese cedar, and that rabbit antisera against Arizona cypress *(C. arizonica)* and incense cedar *(Libocedrus decurrens)* reacted with Japanese cedar extracts in gel diffusion experiments.

Effectiveness for skin test diagnosis. Horiguti and Saito (Ref. 173) reported 28 patients with hay fever in the Japanese cedar pollen season. All 28 had positive dry pollen eye tests, and 25 had positive dry pollen nose challenge tests. Twenty-five of the 28 had positive intradermal skin tests to 1:1,000 dilution extracts of the Japanese cedar pollen extract. Passive transfer tests were positive in five out of five of these patients. No other skin tests with these extracts were reported in nonallergic controls. The Japanese cedar pollen extracts were obtained from Torii Co., Limited, Tokyo.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with Japanese cedar pollen extracts will reduce symptoms of Japanese cedar pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Horiguti and Saito (Ref. 173) reported that immunotherapy with Japanese cedar pollen extracts reduced symptoms of pollinosis in Japanese cedar pollinosis patients, but did not supply data from controlled studies to prove that the relief was due to Japanese pollen extract rather than to other factors.

Recommendations. The Panel recommends that extract of *Cryptomeria japonica* pollen be placed in Category I for skin test diagnosis and in Category IIIA for immunotherapy.

(5) *Other Coniferae pollens.* Other *Coniferae* pollens include the pines, firs, spruces, larches, bald cypress, sequoias, and yews. Most species shed enormous quantities of pollen which is carried for great distances by the wind and which is almost invariably nonallergenic (Refs. 43, 44, 45, 57, 73, and 151). Very rare cases of allergy to pine pollen have been described (Refs. 43 and 57). The Panel found no study of the antigens and allergens in these other *Coniferae* pollens or of their relationships and cross-reactions with antigens and allergens in other species of pollens.

Effectiveness for skin test diagnosis. Rowe (Ref. 57) has described one patient who had asthma and hay fever each year at a time when he was exposed to pine pollen and who had positive scratch tests to nine different species of pine pollen extracts. Immunotherapy with yellow and tamarack pine pollen extracts was considered helpful, but no controls were employed.

Direct eye tests with pine pollen are nearly always negative and therefore pine pollen has been used as control pollen in the dry pollen eye test (Refs. 64 and 153).

Vaughan states that he has seen several cases with positive conjunctival reactions to pine pollen (Ref. 64). Scheppegrell (Ref. 73) states, "The pines which generate pollen in enormous quantities do not cause hay fever. This is not due to the fact that the protein of this pollen is negative in hay fever as we have had many positive reactions in patients tested with an extract of the pollen."

Effectiveness for immunotherapy. Rowe's experience in one case is discussed above. The Panel has found no controlled studies which indicate that immunotherapy with these other *Coniferae* extracts will relieve symptoms of pollinosis better than placebo, or will induce changes in appropriate IgG or IgE antibodies.

Recommendations. The Panel has found only circumstantial and somewhat contradictory evidence indicating that these other *Coniferae* pollen extracts are effective for skin test diagnosis and immunotherapy of Conferae pollinosis and recommends that extracts of other *Coniferae* pollens be placed in Category IIIA for both skin test diagnosis and immunotherapy.

13. *Arecaceae family—Phoenix dactylifera* or date palm is the prototype of this family Date palms grow in the southern parts of the United States from coast-to-coast in the Caribbean Islands and Hawaii (Refs. 43 through 45, 59, 60, and 64). They may pollinate through most of the year. Allergic persons may have hay fever following exposure to the pollen (Refs. 43, 44, 58, 59, 60, 64, and 151).

Royal palm *(Roystonea regia)* pollen has been reported to cause hay fever in Cuba (Ref. 60). Other palms such as the coconut palm *(Cocus nucifera)* and cabbage palm *(Sabal)* produce pollen in sufficient quantities to be considered as possible causes of hay fever but cases attributed to the pollen have not been reported (Ref. 43, 44, and 58). The Panel found no study of the antigens and allergens in palm pollen or of their relationships and cross-reactions with antigens and allergens in other species of pollens.

Effectiveness for skin test diagnosis. The Panel found no controlled studies of the diagnostic use of palm pollen extracts in patients with palm pollinosis.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with palm pollen extracts will reduce symptoms of palm pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. The Panel recommends that extracts of *Arecaceae* pollens be placed in Category IIIA both for skin test diagnosis and immunotherapy.

14. *Casuarinaceae family—Casuarina* or Australian pine is the prototype pollen and the only genus of the family. This native of Australia is found in southern Florida, southern California, Puerto Rico and Cuba. These trees shed copious amounts of wind-borne pollen in various seasons of the year including winter, spring and late summer. Allergic persons may have hay fever and/or asthma after exposure to this pollen (Refs. 43 through 45, 61 through 63, and 151). The Panel found no study of the antigens and allergens in *Casuarina* pollen or of their relationships and cross-reactions with antigens and allergens in other species of pollens.

Effectiveness for skin test diagnosis. The Panel found one reported study of the diagnostic use of *Casuarina* pollen extracts in patients with *Casuarina* pollinosis (Ref. 62). Three patients with either hay fever or asthma during the *Casuarina* pollen season had strongly positive skin reactions to *Casuarina* pollen extracts. Passive transfer tests were attempted with sera of two of those patients and were positive with both. One patient had a positive out-of-season nasal provocation test done with dry pollen. The author knew of a fourth patient studied by another physician who had an increase in asthma during the *Casuarina* pollen season and positive direct skin tests and passive transfer tests with *Casuarina* extracts.

Effectiveness for immunotherapy. The Panel has found no controlled studies which indicate that immunotherapy with *Casuarina* pollen extracts will reduce symptoms of *Casuarina* pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies. Uncontrolled studies suggest, but do not prove, that such immunotherapy might be helpful for patients with Australian pine pollinosis (Refs. 61 and 63).

Recommendations. The Panel recommends that *Casuarina* pollen extract be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

15. *Salicaceae family*—a. *Salix or willow.* Willows are found throughout the temperate parts of North America and also in Europe, Africa and Asia. Though insect pollinated primarily, they are wind pollinated to some extent, and pollen slides may show much willow pollen. Though each species of willow has a relatively short flowering period, there are so many species that the willow season may last for more than two months from March to June or later. All available evidence indicates that willow pollen is of minor importance as a cause of hay fever (Refs. 43 through 45, 64, and 151). The Panel found no study of the antigens in willow pollen or of their relationships and cross-reactions with antigens in other species of pollen.

Effectiveness for skin test diagnosis. The Panel found no controlled studies of the diagnostic use of willow pollen extracts in patients with willow pollinosis.

Effectiveness of immunotherapy. The Panel found no controlled studies indicating that immunotherapy with willow pollen extracts will reduce symptoms of willow pollinosis better than placebo, or will induce changes in specific IgG or IgE Antibodies.

Recommendations. The Panel recommends that extracts of *Salix* species pollens be placed in Category IIIA for both skin test diagnosis and immunotherapy.

b. *Populus or poplar, aspen, and cottonwood.* Poplars are found all over the temperate parts of North America and also in Europe, Northern Africa and Asia. Well known species include the aspen (*P. tremuloides*) and the cottonwood (*P. deltoides*). The Lombardy poplar (*P. nigra*) and white or silver poplar (*P. alba*) are natives of the old world which have been widely planted all over the world as shade or border trees and usually pollinate between April and May. All may cause pollinosis (Refs. 42 through 45, 64, 66, 73, 123, 151, and 153). Tuft and Blumstein (Ref. 153) have reported studies of the relation of white and Carolina poplar using passive transfer tests done with the sera of three clinically sensitive, skin test positive poplar pollinosis patients. All direct passive transfers were positive in varying degrees to both species of the same family. When the reagins in the passively sensitized site were exhausted with one of the poplar pollen extracts, it did not react to the other member of the family. Test tube neutralization of the patients' sera with either of the species of poplar resulted in negative passive transfer reactions to

the other species of poplar. In this manner the close relationship of these two species of poplar pollen was proved.

Effectiveness for skin test diagnosis. The Panel found two reported studies of the diagnostic use of poplar pollen extracts in patients with poplar pollinosis. Tuft and Blumstein (Ref. 153) reported eight patients with hay fever in the poplar pollen season who had positive skin reactions to poplar pollen extracts; dry pollen eye tests were positive in six of these patients; dry pollen nose tests were also positive in six. Passive transfer tests were positive in three. Negative skin reactions to poplar pollen extracts were obtained in 20 of 20 control patients without evidence of pollinosis. Extracts were made by the authors. The pollen was extracted with Coca's solution and standardized by the total nitrogen method. Patients were tested with 0.01 and if negative 0.1 mg of nitrogen per cc by the intradermal method.

Pojevic (Ref. 123) reported six patients with pollinosis in the poplar pollen season of whom two had asthma and four had hay fever. All were exposed to white poplar pollen during the time of their pollinosis symptoms. All had positive skin tests to white poplar pollen extracts. Negative skin reactions to white poplar pollen extracts were obtained in 50 of 50 patients who lived in an area where there was no poplar pollen. Poplar pollen extracts were made by the author. Details of extract manufacturing and skin testing were not described.

Effectiveness for immunotherapy. The Panel found no controlled studies indicating that immunotherapy with poplar pollen extracts will reduce symptoms of poplar pollinosis better than placebo, or will induce changes in specific IgG or IgE antibodies.

Recommendations. The Panel recommends that extracts of *Populus* species pollens be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

16. *Juglandaceae family*—a. *Juglans (walnuts).* There are at least seven species of Juglans or walnuts in the Untied States. The common walnuts in the eastern United States are the black walnut (*J. nigra*), the butternut (*J. cinerea*), and the English walnut (*J. regia*). These shed pollen in enormous quantities in late May and early June, but rarely cause hay fever. The California black walnut (*J. californica*) sheds large amounts of pollen in California in April, May and early June and may be a most important cause of spring hay fever (Refs. 42 through 45, 64 through 66, 73, 75, 118, 151, 154, and 157). The Panel found no study of the antigens in walnut pollens or of their relationships and cross-reactions with antigens in other species of pollens.

Effectiveness for skin test diagnosis. Bernton (Ref. 154) reported one patient with clinical evidence of black walnut pollen hay fever who had a skin reaction to black walnut pollen extract.

Hall (Ref . 65) reported 20 patients with clinical evidence of black walnut pollen hay fever who had positive skin tests to black walnut pollen extracts. In all 12 patients tested, hay fever symptoms were induced by direct application of dry pollen to the nostrils. Controls (number not stated) had no skin reactions to the black walnut pollen extract.

Effectiveness of immunotherapy. The Panel found no controlled studies of immunotherapy with black walnut pollen extracts.

Recommendations. The Panel recommends that extracts of *Juglans nigra* and *J. californica* pollens be placed in Category I for skin test diagnosis and in Category IIIA for immunotherapy. Other *Juglans* species should be placed in Category IIIA for both skin test diagnosis and immunotherapy.

b. *Carya or hickory.* The pecan (*C. pecan*) is the most important hickory pollen. This tree occurs in the south central United States from North Caroline to Florida and west to Texas and Oklahoma and is extensively cultivated. It produces a large amount of pollen from mid-April to May which causes much hay fever and asthma. Wodehouse states that in areas where it is cultivated, it causes a great deal of hay fever, often ranking next in importance to ragweed (Ref. 43). Other hickories are responsible for hay fever in the Middle Atlantic States and include shellbark hickory (*C. ovata*), white heart hickory (*C. glabra*), and nutmeg hickory (*C. myristicaeformis*) (Refs. 42 through 45, 64, 66, 154, 156, and 157). Thommen (Ref. 42) reported three patients sensitive to hickory pollen who gave positive skin reactions when tested with five different species of hickory pollen. The names of the species were not stated. Wodehouse (Ref. 43) states that in hay fever studies the various species of hickory are not generally distinguished from each other because allergens in their pollens are believed to interact more or less perfectly. Otherwise, the Panel found no reports of studies of the antigens in pecan or hickory pollens or of their relationships and cross-reaction with antigens in other species of pollens.

Effectiveness for skin test diagnosis. The Panel found several reports of the diagnostic use of hickory pollen extracts in patients supected of having hickory pollinosis. Bernton (Ref. 154) reported seven patients with hickory pollen hay fever who had positive skin tests to hickory pollen extracts.

Tuft and Blumstein (Ref. 153) reported four patients with hay fever in the hickory pollen season who had positive skin tests to hickory pollen extracts. Dry hickory pollen eye and nose tests were negative in all four of these patients. Negative skin reactions to hickory pollen extract wre obtained in 20 of 20 control patients without evidence of pollinosis. Extracts were made by the authors. The pollen was extracted with Coca's solution and standardized by the total nitrogen method. Patients were tested with 0.01 and, if negative, 0.1 mg of nitrogen per cc by the intradermal method.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with hickory pollen extracts.

Recommendations. The Panel recommends that extracts of *Carya* species be placed in Category I for skin test diagnosis and in Category IIIA for immunotherapy.

17. *Betulacea family*—a. *Betula or birch.* Birches are found mainly in the northern parts of the United States and in Canada and also in Northern Europe and Asia. Common species include the white birch (*B. populifolia*), black or cherry birch (*B. lenta*), yellow birch (*B. lutea*), river or red birch (*B. nigra*) which may be found in the southern United States as well as in the north, and paper birch (*B. papyrifera*). In northeastern United States and Canada, birches pollinate in late April and early May shedding large amounts of pollen which is highly allergenic and known to cause hay fever and asthma (Refs. 42 through 45, 64, and 151). Thommen (Ref. 42) reported five patients sensitive to birch pollen who gave position skin reactions when tested with six different species of birch pollen. The names of the species tested were not given.

Belin (Refs. 95 and 120), using immunodiffusion, passive hemagglutination-inhibition, and radioallergosorbent techniques, has shown antigenic relationships but not complete identity between birch pollen, alder pollen, aspen pollen, hazel pollen, and hazelnut extracts. The antigenic relationship was closest between birch and alder pollens. He found at least two major allergens in birch pollen extract with molecular weights around 20,000 daltons. Both allergens were antigenically similar, but of different electrical charge in electrophoretic

studies. They were heat stable, resisting 100° C for 15 minutes, and acid stable, resisting pH 2 for 32 hours. He found other substances in crude birch pollen extracts which were antigenic for experimental animals but not allergenic in man, were of larger molecular weight, and were destroyed by heating to 100° C for 15 minutes. The active allergens were released rather quickly from whole birch pollen grains during the process of extraction, in contrast to the slower release of the thermolabile, non-allergenic antigens.

Effectiveness for skin test diagnosis. The Panel found six reported studies of the diagnostic use of birch pollen extracts in patients with birch pollinosis. Bernton (Ref. 154) reported three patients with hay fever in the birch pollen season who had positive skin tests to birch pollen extracts.

Tuft and Blumstein (Ref. 153) reported eight patients with hay fever in the birch pollen season who had positive skin reactions to birch pollen extracts; dry pollen eye tests were positive in two of these patients; dry pollen nose tests were negative in all. Negative skin reactions to birch pollen extracts were obtained in 20 of 20 control patients without evidence of pollinosis. Extracts were made by the authors. The pollen was extracted with Coca's solution and standardized by the total nitrogen method. Patients were tested with 0.01 mg and, if negative, 0.1 mg of nitrogen per cc by the intrademal method.

Zetterstrom, Fagerberg, and Wide (Ref. 103) reported 10 patients with rhinitis symptoms in the birch pollen season, 4 of whom also had asthma. All had positive skin reactions to birch pollen extract. All 10 had positive nasal challenge tests with birch pollen extract. All had positive radioallergosorbent tests to birch pollen extract. Negative skin tests in nonallergic control were not reported.

Aas and Johansson (Ref. 92) reported 29 untreated patients who "suffered from immediate type allergy to more than one substance resulting in bronchial asthma and other symptoms." Seven had positive bronchial provocation tests with birch pollen extract or positive dry pollen nose or eye challenge tests; 22 had negative provocation tests. Of the 7 patients with positive provocation tests, 57 percent had positive case histories and skin tests to birch pollen extracts and 86 percent had positive radioallergosorbent tests to birch pollen extracts. Of the 22 patients with negative provocation tests, all had negative case histories and skin tests to birch pollen extracts and 73 percent had negative radioallergosorbent tests to birch pollen extracts. Dry pollen was obtained from Cernelle AB, Sweden; extracts were obtained from Nyegaard and Company, Oslo, Norway.

Ahlstedt, Eriksson, Lindgren and Roth (Ref. 93) reported 21 patients with positive nasal provocation tests to birch pollen extracts. Nineteen of these had positive skin tests to birch pollen extracts, and 19 had positive radioallergosorbent tests. Eleven patients had negative nasal provocation tests with birch pollen extracts. 9 of these had negative skin tests to birch pollen extracts, and 8 had negative radioallergosorbent tests to birch pollen extracts. Extracts were obtained from Pharmacia AB.

Belin (Refs. 95 and 120) reported 38 patients with clinical evidence of allergy to birch pollen who had positive skin tests to birch pollen extracts. Passive transfer tests were done with the sera of 3 of these patients and were positive in each instance. Skin tests were negative in the two nonallergic patients used as recipients for the passive transfer tests. Pollen was usually obtained from Cernelle, Vegeholm, Sweden, and was extracted by the author with phosphate buffered saline at 1:4 or 1:10 w/v.

Effectiveness for immunotherapy. Ahlstedt, Belin, Eriksson, and Hanson (Ref. 121) studied the effects of immunotherapy with alumprecipitated birch pollen extracts on seven patients with birch pollen allergy manifested by "typical history," positive skin tests and positive nasal provocation tests. Alum-precipitated, pyridine extracted extracts from Dome Laboratories, England were given for 6 months. Maintenance dosage was reached in 8 to 9 weeks and then given every 6 to 8 weeks. Six of the 7 patients showed diminution in their response to nasal challenge with birch pollen extract. Of the six who improved, two showed a decrease in IgE antibodies to birch pollen and a rise in non-IgE (presumably IgG) antibodies to birch pollen, while four showed a rise in IgE antibodies, with little rise in non-IgE antibodies to birch pollen. The one patient who had no diminution in response to nasal challenge had insignificant changes in both IgE and IgG antibodies to birch pollen. Six nonallergic patients had no IgE or non-IgE antibodies to birch pollen. No nonallergic patients were treated with birch pollen extracts, and no birch pollinosis patients were treated with placebo.

No studies employing aqueous extracts of birch pollen for immunotherapy were found.

Recommendations. The reported results of skin testing with birch pollen extracts indicate that these extracts are effective for skin test diagnosis of birch pollinosis. The reported results of immunotherapy are too scanty and uncontrolled to be conclusive but demonstrate that the techniques are available to demonstrate a conclusive difference in nasal response to challenge with birch pollen extracts and in serum IgE and IgG antibodies between treated and untreated patients with birch pollinosis. The Panel recommends that extracts of *Betula* species pollens be placed in Category I for skin test diagnosis and in Category IIIA for immunotherapy.

b. *Alnus or alder.* Alders are found throughout most of the United States and Canada. They flower very early, usually in March or April, and even in January and February in the southern states. Large amounts of pollen are shed and may cause hay fever (Refs. 42 through 44, 64, and 151). Thommen (Ref. 42) reported two patients sensitive to alder pollen who gave positive skin reactions when tested with three different species of alder pollen. The names of the species were not stated.

Belin (Ref. 95), using immunodiffusion, passive hemagglutination-inhibition, and radioallergosorbent techniques has shown antigenic relationships but not complete identity between alder, birch, aspen, and hazel pollen extracts. The antigenic relationship was closest between alder and birch extracts.

Effectiveness. The Panel found no controlled studies of the diagnostic or immunotherapeutic use of alder pollen extracts in patients with alder pollinosis.

Recommendations. The Panel recommends that extracts of *Alnus* species pollens be placed in Category IIIA for both skin test diagnosis and immunotherapy.

c. *Carpinus or hornbeam—Carpinus caroliniana* (American hornbeam, blue beech, water beech, ironwood) is the prototype of the genus. This is the only species native to North America and is common in the eastern United States in moist woods and along streams from Nova Scotia to Minnestoa and southward to Florida and Texas. *C. betula,* the European hornbeam, is commonly planted in North America. Hornbeams shed airborne pollen in April and May which may cause hay fever (Refs. 43, 44, and 64). The Panel found no study of the antigens and allergens in hornbeam pollen or of their relationships and cross-reactions with antigens and allergens in other species of pollens.

Effectiveness. The Panel found no controlled studies of the diagnostic or immunotherapeutic use of hornbeam

pollen extracts in patients with hornbeam pollinosis.

Recommendations. The Panel recommends that extracts of *Carpinus* pollens be placed in Category IIIA for both skin test diagnosis and immunotherapy.

d. *Ostrya or hop-hornbeam or ironwood—O. virginiana* (hop-hornbeam, ironwood, leverwood, or hardhack) trees are commonly found from Cape Breton Island to Manitoba and southward to Florida and Texas. They flower in April or May producing large amounts of pollen which may cause hay fever (Refs. 43, 44, 64, and 151). The Panel found no study of the antigens and allergens in hop-hornbeam pollen or of their relationships and cross-reactions with antigens and allergens in other species of pollens.

Effectiveness. The Panel found no controlled studies of the diagnostic or immunotherapeutic use of hop-hornbeam pollen extracts in patients with hop-hornbeam pollinosis.

Recommendations. The Panel recommends that extracts of *Ostrya* pollens be placed in Category IIIA for both skin test diagnosis an immunotherapy.

e. *Corylus or hazel or filbert.* The genus includes three species which are native to North America. *C. americana* (American hazel) and *C. rostrata* (beaked hazel) are found throughout most of the United States; *C. californica* (California hazel) is found on the Pacific Coast from British Columbia to California. The European species (*C. avellana*), the common hazelnut or filbert, is the one most frequently planted in the United States for fruit and ornament. Hazels produce airborne pollen in March and April which may cause hay fever (Refs. 42 through 44, 64, and 151). Belin (Ref. 95), using immunodiffusion, passive hemagglutination-inhibition, and radioallergosorbent techniques, has shown antigenic relationships but not complete identity between hazel, birch, alder, and aspen pollen extracts. The antigenic relationship was closest between alder and birch pollen extracts.

Effectiveness. The Panel found no controlled studies of the diagnostic or immunotherapeutic use of hazel pollen extracts in patients with hazel pollinosis.

Recommendations. The Panel recommends that extracts of *Corylus* pollens be placed in Category IIIA for both skin test diagnosis and immunotherapy.

18. *Myricaceae family—Myrica cerifera* or wax myrtle is the prototype pollen for the *Myricaceae* family. Wax myrtle is found along the Atlantic coast from New Jersey to Florida, on the Gulf coast and in Bermuda (Refs. 43, 44, and 69). These small trees and shrubs shed large quantities of airborne pollen in the early spring (Ref. 69). Their role in hay fever is not fully understood and is complicated by the fact that their pollen on pollen slides is very difficult to distinguish from that of the *Betulaceae* family (birches, alders, etc.) (Refs. 43 and 44). Their pollen has been suspect as a cause of hay fever in Florida (Ref. 43). The Panel found no study of the antigens and allergens in wax myrtle pollen or of their relationships and cross-reactions with antigens and allergens in other species of pollens.

Effectiveness. Wax myrtle pollen extracts are not discussed in the reports which discuss wax myrtle pollen (Refs. 43, 44, and 69). The Panel found no reports of the diagnostic or immunotherapeutic use of wax myrtle pollen extracts in patients with wax myrtle pollinosis.

Recommendations. The Panel recommends that extracts of *Myricaceae* pollens be placed in Category IIIA for both skin test diagnosis and for immunotherapy.

19. *Fagaceae family.*—a. *Quercus or oak.* The oaks are widely distributed in the Northern hemisphere. There are many species including black oak (*Q. velutina*), red oak (*Q. rubra*), pin oak (*Q. palustris*), willow oak (*Q. Phellos*), white oak (*Q. alba*), chestnus oak (*Q. Prinus*), live oak (*Q. agrifolia*) and scrub oak (*Q. ilicifolia*). Oaks shed enormous amounts of pollen, usually in the month of May. Because of the slightly different pollinating seasons of different species of oaks, the total oak pollinating season in a given area may be long. The pollen may cause hay fever or asthma (Refs. 42 through 45, 64, 151, and 153).

Thommen (Ref. 42) reported 8 patients sensitive to oak pollen who gave positive skin reactions when tested with 21 different species of oak pollen. The names of the species were not stated.

Tuft and Blumstein (Ref. 153) reported studies of the relation of white, swamp, red, pin, and scarlet oak using passive transfer tests done with the serum of one clinically sensitive, skin test positive oak pollinosis patient. All direct passive transfers were positive in varying degrees to "several" species of the same family. When the reagins in a passively sensitized site were exhausted with one of the oaks, it did not react to the other members of the family. Test tube neutralization of the patient's serum with extract from one of the species of oak resulted in negative passive transfer reactions to all of the other species of oak. In this manner, the close relationship of these five species of oak pollen was proven.

Furuya (Ref. 109) reported cross-reactions between different species of oak pollen. His data are discussed in the section on effectiveness for skin test diagnosis which follows.

Effectiveness for skin test diagnosis. Thommen (Ref. 42) reported one patient with hay fever and asthma occurring only in the oak pollen season. "Skin tests showed a marked sensitivity to oak pollen alone."

Tuft and Blumstein (Ref. 153) reported four patients with hay fever in the oak pollen season who had positive skin reactions to oak pollen extracts; dry pollen eye tests were positive in one out of four of these patients; dry pollen nose tests were positive in one out of four. Passive transfer tests were positive in one (see section on specificity). Negative skin reactions to oak pollen extracts were obtained in 20 of 20 control patients without evidence of pollinosis.

Zetterstrom, Fagerberg, and Wide (Ref. 103) reported 10 patients with rhinitis symptoms in the oak pollen season, 4 of whom also had asthma. All had positive skin reactions to oak pollen extract. Eight patients had positive and 2 had negative nasal challenge tests with oak pollen extract. Five had positive, four had equivocally positive, and one had negative radioallergosorbent tests to oak pollen extract. Negative skin tests in nonallergic controls were not reported.

Furuya (Ref. 109) reported four patients with rhinitis and/or asthma in the oak pollen season who had exposure to oak pollen. All had positive skin tests to oak pollen extracts with four of the four patients reacting to *Q. glauca*, three of four to *Q. acutisima*, three of four to *Q. serratea*, and two of four to white oak. Passive transfer tests were positive with extracts of *Q. glauca*, *Q. actuisima*, and *Q. serrata* in three patients, and with *Q. glauca* only in one patient. Passive transfer neutralization tests were done with the sera of the three patients who had positive passive transfer reactions to all three species of oak, and it was found that each would neutralize antibodies to the two others. Eye challenge tests were positive in three of four patients. The patient with the negative eye challenge test had asthma without symptoms of hay fever, and the bronchial challenge test was positive. Negative skin tests to the oak pollen extracts were obtained in 175 nonallergic patients. The white oak pollen extract was obtained from Hollister-Stier Laboratories; the other extracts were prepared by the author.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with oak pollen extracts.

Recommendations. The Panel recommends that extracts of *Quercus* species pollens be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

b. *Fagus or beech—F. granifolia* or American beech is native to North America and grows from Nova Scotia to Florida and west to Missouri and Texas. European beech or *F. sylvatica* is frequently cultivated in the United States. Beech trees bloom in late spring and early summer and shed large amounts of airborne pollen which causes some hay fever (Refs. 42 through 45, 64, 66, 151, and 153). The Panel found no study of the antigens in beech pollens or of their relationships and cross-reactions with antigens in other species of pollens.

Effectiveness for skin test diagnosis. Tuft and Blumstein (Ref. 153) reported six patients with hay fever in the beech pollen season who had positive skin reactions to beech pollen extracts. Dry pollen eye tests were positive in one of these patients; dry pollen nose tests were positive in none. Negative skin reactions to beech pollen extracts were obtained in 20 of 20 control patients without evidence of pollinosis.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with beech pollen extracts.

Recommendations. The Panel recommends that beech pollen extracts be placed in Category IIIA for both skin test diagnosis and for immunotherapy.

20. *Ulmaceae family*—a. *Ulmus or elm. Ulmus amricanus* or American elm is the prototype species of the *Ulmaceae* family. There are many other species including slippery elm (*U. rubra* and *U. fulva*), English elm (*U. campestris*), Chinese elm (*U. pumila*), cedar or scrub elm (*U. crassifolia*), September or red elm (*U. serotina*), cork elm (*U. racemosa*), winged elm (*U. alata*), water elm (*Planera*) and others. These are widely distributed over most of the temperate and northern regions of the Northern Hemisphere. They shed large amounts of pollen of high allergenic toxicity. Most species pollinate in the very early spring: two, *U. crassifolia* and *U. serotina*, pollinate in August, September, and October (Refs, 42 through 45, 64, 66, 73, and 151). Thommen (Ref. 42) reported three patients sensitive to elm pollen who gave positive skin reactions when tested with three different species of elm pollen. The names of the species were not stated. Otherwise, the Panel found no study of the antigens in elm pollen or of their relationships and cross-reactions with antigens in other species of pollen.

Effectiveness for skin test diagnosis. Bernton (Ref. 154) reported one patient with elm pollen hay fever who had a positive skin test to elm pollen extract.

Black and Durham (Ref. 155) reported six patients clinically sensitive to elm pollen who had positive skin tests to elm pollen extract.

Tuft and Blumstein (Ref. 153) reported six patients with hay fever in the elm pollen season who had positive skin reactions to elm pollen extracts; dry pollen eye tests were positive in all six of these patients; dry pollen nose tests were positive in three. Negative skin reactions to elm pollen extracts were obtained in 20 of 20 control patients without evidence of pollinosis.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with elm pollen extracts.

Recommendations. The Panel recommends that extracts of *Ulumus* species pollen by placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

b. *Celtis or hackberry.* The common hackberry (*C. occidentalis*) produces the prototype pollen. This tree is found from Quebec to North Carolina and westward to Manitoba and Missouri. The southern hackberry (*C. laevigata*) is found from Virginia to Florida and west to southern Illinois and Texas. These North American hackberries usually pollinate in April and May and may be an occasional cause of hay fever (Refs. 42 through 45, and 64). The tala) is reported to be a very important cause of hay fever in Argentina during its pollination season between September and November (Refs. 43, 44, 80, 167, and 168). The Panel found no study of the antigens in *Celtis* pollens or of their relationships and cross-reactions with antigens in other species of pollens.

Effectiveness for skin test diagnosis. Carron (Ref. 167) reports four patients with positive skin tests to *C. talis* extracts, with positive passive transfer tests in each of the three patient tested.

Walker and Carron (Ref. 80) studied 47 allergic patients with pollen-induced rhinitis or asthma. Positive intradermal reactions occurred in 21 of these patients following a dose of 100 Stull-Cooke units of a purified *C. talis* extract. Four patients had 1-plus reactions, 10 had 2-plus, 6 had 3-plus reactions, and 1 was a questionable-positive. Seventeen of these 21 patients were positive by passive transfer testing; the 1 questionably positive patient gave a negative passive transfer; and 3 were not tested.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with *Celtis* pollen extracts.

Recommendations. The Panel recommends that extracts of *Celtis* pollens be placed in Category IIIA for both skin test diagnosis and immunotherapy.

21. *Oleaceae family*—a. *Fraxinus or ash.* White ash (*F. americana*) is the prototype species of the ashes. There are many other species including red ash (*F. pennsylvanica*), green ash (*F. pennsylvanica lanceolata*), mountain ash (*F. texana*), Arizona ash (*F. velutina*), and Oregon ash (*F. oregona*). Ash trees occur all over the United States and Canada; are being increasingly as city street trees, and produce enormous quantities of pollen per tree usually in March or April, which may cause hay fever (Refs. 42 through 45, 64, 66, 73, 74, 81, 82, 151, 153, and 155). The Panel found no study of the antigens in ash pollens or of their relationships and cross-reactions with antigens in other species of pollens.

Effectiveness for skin test diagnosis. The Panel found two reported studies of the diagnostic use of ash pollen extracts in patients suspected of having ash pollinosis. Bernton (Ref. 154) reported one patients with clinical evidence of ash-pollen hay fever who had a skin reaction to ash-pollen extract.

Tuft and Blumstein (Ref. 153) reported 13 patients with hay fever in the ash pollen season who had positive skin reactions to ash pollen extracts. Dry pollen eye tests were positive in one of these patients; day pollen nose tests were positive in one. Negative skin reactions to ash pollen extract were obtained in 20 of 20 control patients without evidence of pollinosis.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with ash pollen extracts.

Recommendations. The Panel recommends that extracts of *Fraxinus* species pollens be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

b. *Olea europaea or cultivated olive.* The olive tree is extensively grown for its fruit in California, Arizona, and in the Mediterranean countries. Though primarily insect pollinated, it is partly wind pollinated and may scatter large amounts of pollen in April and May which may cause hay fever (Refs. 43 through 45, 70 through 72, 81, and 82). The Panel found no study of the antigens in olive pollens or of their

relationships and cross-reactions with antigens in other species of pollens.

Effectiveness for skin test diagnosis. Kessler (Ref. 71), in a very brief report, described 100 patients with allergy to olive pollen manifested by seasonal rhinitis, conjunctivitis, and asthma. The diagnosis was "confirmed by cutaneous and intracutaneous skin tests, by passive transfer, and finally by clinical experience" (symptoms of pollinosis when visiting the pollinating olive groves which clear after leaving the groves).

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with olive pollen extracts. Kessler (Ref. 71) implied that olive pollen extracts are effective for immunotherapy of olive pollinosis, but did not provide evidence from controlled studies.

Recommendations. The Panel recommends that extract of olive pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

c. *Ligustrum or privet.* Privet is abundant in the eastern United States and particularly in the southeast, and may also be found in Europe, Asia, Australia, and South America. Though primarily insect pollinated, it may be partly air pollinated and shed quantities of pollen in June which may cause hay fever (Refs 43, 44, 64, 73, and 151). The Panel found no study of the antigens in privet pollen or of their relationships and cross-reactions with antigens in other species of pollens.

Effectiveness for skin test diagnosis. Scheppegrell (Ref. 73) reported 20 patients with hay fever symptoms following exposure to flowering privet. Pollen test plates were exposed at their residences and showed the presence of large amounts of privet pollen in 17 of the 20 cases. "Practically all" of the 20 patients showed a positive skin reaction to privet pollen extract. No skin tests with privet pollen extracts in nonallergic control patients were reported.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with privet pollen extracts.

Recommendations. The Panel recommends that extracts of *Ligustrum* species pollen be placed in Category IIIA for both skin test diagnosis and immunotherapy.

22. *Platanaceae family—Platanus occidentalis,* or common native sycamore, is the prototype species of the *Platanaceae* family. There are other species such as the oriental plane tree (*P. orientalis*), the London plane tree (*P. acerifolia*), and the western sycamore (*P. racemosa*). These are found throughout the United States, and shed copious amounts of pollen in April and May which may cause asthma or hay fever (Refs. 42 through 45, 64, 66, 73, 75, and 151). The Panel found no study of the antigens in sycamore pollen or of their relationships and cross-reactions with antigens in other species of pollens.

Effectiveness for skin test diagnosis. Bernton (Ref. 154) reported 7 patients with clinical evidence of sycamore pollen hay fever who had skin reactions to sycamore pollen extracts.

Tuft and Blumstein (Ref. 153) reported 6 patients with hay fever in the sycamore pollen season who had positive skin tests to sycamore pollen extracts. Dry pollen eye tests were positive in 2 of these 6 patients; dry pollen nose tests were positive in 1. Negative skin reactions to sycamore pollen extracts were obtained in 20 of 20 control patients without pollinosis.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with sycamore pollen extracts.

Effectiveness for immunotherapy. It is recommended that extracts of *Platanus* species pollens be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

23. *Hamamelidaceae family—Liquidambar styraciflua* or sweet gum is the prototype of this family. These trees are found in the eastern half of the United States and west as far as Oklahoma and Texas. They produce large amounts of pollen between April and May in the north, and between March and April in the south. Whether or not the pollen is allergenic is yet to be determined (Refs. 44, 45, and 64). No study was found on the antigens in sweet gum pollens or of their relationship and cross-reactions with antigens in other species of pollens.

Effectiveness of skin test diagnosis. The Panel found no reported controlled studies of the diagnostic use of sweet gum pollen extracts in patients suspected of having sweet gum pollinosis. Vaughan (Ref. 64) reported that he had observed positive skin reactions to sweet gum pollen extracts, but provided no information about the patients with these skin reactions.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with sweet gum pollen extracts.

Recommendations. It is recommended that extract of *Liquidambar styraciflua* pollen be placed in Category IIIA for both skin test diagnosis and immunotherapy.

24. *Aceraceae family—Acer saccharinum,* or silver maple, is the prototype of the family. There are many other species. Some are strictly insect pollinated, such as the Norway maple (*A. platanoides*), and the sycamore maple (*A. pseudophltanus*). Others are partly pollinated by insects and partly by wind and include the red maple (*A. rubrum*), and the sugar maple (*A. saccharum*), as well as the prototype species. Still others are strictly wind pollinated such as the box elder, or Manitoba maple (*A. negundo*). These maples are found all over the United States and Canada. All shed pollen which may be a cause of asthma and hay fever. Some maples pollinate in the early spring in February and other species at consecutively later times in the spring until June so that a patient may be exposed to maple pollen over a period of several months (Refs 42 through 45, 64, 66, 73, 74, 151, 153, and 154). Thommen (Ref. 42) reported two patients sensitive to maple pollen who gave positive skin reactions when tested with five different species of maple pollen. The names of the species were not stated. Otherwise, the Panel found no study of the antigens in maple pollen or of their relationships and cross-reactions with antigens in other species of pollen.

Effectiveness of skin test diagnosis. Bernton (Ref. 154) reported three patients with maple pollen hay fever who had skin reactions to maple pollen extracts.

Tuft and Blumstein (Ref. 153) reported 14 patients with hay fever in the maple pollen season who had positive skin reactions to maple pollen extracts. Dry pollen eye tests were positive in 11 of these 14 patients; dry pollen nose tests were positive in 3. Negative skin reactions to maple pollen extracts were obtained in 20 of 20 control patients without pollinosis.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with maple pollen extracts.

Recommendations. It is recommended that extracts of *Acer* species pollens be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

25. *Tiliaceae family—Tilia americana,* the American linden or basswood, is widely distributed in northern, central, eastern, and southeastern United States and Canada. The European linden (*T. europaea*) is frequently cultivated in and near cities as a shade tree. Though insect pollinated, these trees are copious pollen shedders in the early summer, and their pollen can be demonstrated in the air at a considerable distance from the trees. Their pollen may occasionally

cause hay fever (Refs. 43 and 84). The Panel found no study of the antigens and allergens in linden pollen or of their relationships and cross-reactions with antigens and allergens in other species of pollens.

Effectiveness for skin test diagnosis. In one reported study of the diagnostic use of linden pollen extract, Derbes (Ref. 84) reported four patients with hay fever and/or asthma during the linden pollen season. All four had positive skin, conjunctival, and passive transfer tests to linden pollen extract.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with linden pollen extracts.

Recommendations. It is recommended that extracts of *Tilia* species pollens be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

26. *Mimosaceae family*—a. *Acacia or acacia.* Acacia is found mainly in California. This is primarily, if not entirely, insect pollinated: pollen is produced sparingly and is not easily carried by the wind. Nevertheless, it causes hay fever and asthma in sporadic cases (Refs. 43 through 45, 64, and 76). No study was found on the antigens in acacia pollen or of their relationships and cross-reactions with antigens in other species of pollens.

Effectiveness. The Panel found no controlled studies of the diagnostic or immunotherapeutic use of acacia pollen extracts in patients with acacia pollinosis.

Recommendations. It is recommended that extracts of acacia pollens be placed in Category IIIA both for skin test diagnosis and immunotherapy.

b. *Prosopis or mesquite.* The honey mesquite (*P. juliflora*, syn. P. glandulosa) is the prototype of this genus. It is found in the arid regions of the Southwestern United States. It is also found in Hawaii, Mexico, and South America. It flowers from May to July and is undoubtedly insect pollinated, but much pollen is also distributed by the wind. It is responsible for hay fever and asthma in areas where it is abundant (Refs. 43 through 45, 58, 59, 64, 77, 78, and 151). The Panel found no study of the antigens and allergens in mesquite pollen or of their relationships and cross-reactions with antigens and allergens in other species of pollens.

Effectiveness for skin test diagnosis. Sellers (Ref. 77) reported 10 patients with hay fever symptoms after exposure to mesquite pollen who had positive scratch tests with mesquite pollen extract. Five of these patients were thought to be sensitive to mesquite pollen only; five were thought to be sensitive to mesquite and other pollens. Twelve patients not suffering from hay fever had negative skin reactions to mesquite pollen extracts. The pollen extract was made by the author and was a 1:5 w/v extract of mesquite pollen in two parts of glycerine to one part of Coca's solution.

Ordman (Ref. 78) reported one patient with hay fever and asthma symptoms after exposure to mesquite pollen who had positive skin tests with mesquite pollen extract. He stated that he had seen many similar cases of mesquite pollinosis. He also stated that skin testing with mesquite pollen extract "invariably gives a definitely positive reaction in the clinically sensitive patient." He reported no nonallergic patients with negative skin tests to mesquite pollen.

Novey, Roth, and Wells (Ref. 177) reported eight patients with allergic rhinitis who had exposure to mesquite pollen. All had positive skin tests to mesquite pollen extracts. Nasal challenge tests with mesquite pollen extracts were positive in eight of eight patients, conjunctival challenge in seven of eight, and bronchial challenge in three of six. Radioallergosorbent tests were positive in most or all. When 15 nonatopic individuals were scratch tested by a technique producing three- to four-plus positive reactions in all 8 of the allergic patients, there was no reaction in 13, and only a one-plus reaction in 2. Extracts were obtained from Hollister-Stier Laboratories.

Effectiveness for immunotherapy. The Panel found no controlled studies of immunotherapy with mesquite pollen extracts. Uncontrolled studies suggest, but do not prove, that such immunotherapy might be effective for patients with mesquite pollinosis (Refs. 61 and 63).

Recommendations. It is recommended that extract of *Prosopsis juliflora* pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

27. *Simarubaceae (Ailanthus) family—Ailanthus altissima* or tree of heaven is the prototype of the *Simarubaceae* family. This tree is a native of China, but has become naturalized practically throughout the United States (Refs. 43 and 44). While primarily insect pollinated, much pollen is airborne and is frequently found on pollen slides throughout the month of June (Ref. 43). It is a rare cause of hay fever and asthma (Refs. 43, 44, 67, and 68). The Panel found no study of the antigens in Ailanthus pollen or of their relationships and cross-reactions with antigens in other species of pollens.

Effectiveness for skin test diagnosis. Blumstein (Ref. 67) reported two patients with hay fever and asthma during the *Ailanthus* pollen season. Both patients had positive skin tests with *Ailanthus* pollen extracts and positive nose and eye tests with dry *Ailanthus* pollen. No skin tests in nonallergic patients were reported. Passive transfer tests were positive with serum from one patient. The *Ailanthus* pollen extract was made by the author, but details of the manufacturing process were not given.

Tas (Ref. 68) reported four patients with hay fever during the *Ailanthus* pollen season who had positive skin tests with *Ailanthus* pollen extract. No skin tests in nonallergic patients were reported.

Effectiveness of immunotherapy. The Panel found no controlled studies of immunotherapy with *Ailanthus* pollen extracts. Blumstein reported that immunotherapy with *Ailanthus* pollen extract appeared to relieve symptoms of hay fever and asthma in his two patients with *Ailanthus* pollinosis (Ref. 67).

Recommendations. It is recommended that extract of *Ailanthus* pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

28. *Moraceae family—Broussonetia papyrifera* (syn. *Papyrius papyrifera*) or paper mulberry produces the prototype *Moraceae* pollen. It is found in the United States throughout the Southeast, and as far north as Pennsylvania, and west to Oklahoma and Texas. The season of pollen dispersal is in the latter part of April of in May. Allergic persons may have hay fever and asthma following exposure to the pollen. *Morus ruba* (red mulberry), and *Morus alba* (white mulberry) are found extensively in the eastern United States and west to South Dakota and Texas and Southern California. These shed large amounts of pollen in May which may occasionally cause hay fever. *Maclura pomifera* (osage orange) is found in the same area. It produces pollen in June which may occasionally cause severe hay fever (Refs. 42 through 44, 55, 56, 64, 66, 102, 151, 154, and 157). The pollen of paper mulberry cross-reacts with those of *Morus* genera (red, white, and black mulberry) and *Maclura* genera (Osage orange) so that a patient sensitive to one will usually react to the other (Refs. 43 and 44).

Bernton (Ref. 55) described a patient with paper mulberry pollinosis who had positive cutaneous reactions to the pollens of paper mulberry, white mulberry, and osage orange, and

positive intradermal reactions to paper mulberry and osage orange extracts.

Targow (Ref. 102) described a patient with white mulberry pollinosis who had positive cutaneous reactions to both white and paper mulberry. Antigenic differences between these three genera are recongized, but not well studied (Ref. 55).

Effectiveness for skin test diagnosis. Bernton (Refs. 55 and 154) has reported three patients with asthma and hay fever following exposure to paper mulberry pollen who had positive skin tests to mulberry pollen. Subcutaneous injection of 5 pollen units produced a large local reaction in 1 patient and symptoms of hay fever. Subcutaneous injection of 11 pollen units in another produced a constitutional reaction. No skin tests with mulberry pollen extracts in nonallergic controls were reported.

Targow (Ref. 102) reported two patients with hay fever and asthma after exposure to white mulberry pollen who had positive cutaneous reactions to white mulberry pollen extract. Both had increase in symptoms when standing under a pollinating white mulberry tree. Otherwise no eye, nose, or bronchial challenge tests were reported. No skin tests with mulberry pollen extracts in nonallergic controls were reported.

Effectiveness for immunotherapy. Both Bernton (Ref. 55) and Targow (Ref. 102) thought that their mulberry pollinosis patients reported above were benefited by immunotherapy with the appropriate mulberry pollen extract, but neither employed controls. The Panel found no controlled studies on immunotherapy with mulberry extracts.

Recommendations. The Panel recommends that extracts of *Broussonetia, Morus,* and *Maclura* species pollens be placed in Category I for skin test diagnosis and in Category IIIA for immunotherapy.

29. *Urticaceae family*—a. *Urtica or nettle. U. gracilis* (syn. *U. dioica*) or great nettle is the prototype pollen. There are other species including the dwarf nettle (*U. urens.*) They are found over much of the United States and in Europe. They shed copious amounts of pollen (Refs. 43 and 44) in late July and August which may cause hay fever (Refs. 88 through 90). The fine size of the pollens leads to underestimating its prevalence in the air unless volumetric samplers are used instead of gravity samplers (Refs. 88 through 90). The Panel found no study of the antigens in nettle pollens or of their relationships and cross-reactions with antigens in other species of pollens. Nettle pollen is said not to cross-react with wall pellitory pollen (Ref. 86).

Effectiveness for skin test diagnosis. Solomon (Ref. 90) has reported that of 420 consecutive atopic patients tested epidermally with 1:20 (w/v) *U. gracilis* extract (source and manufacturing method not described) 2 plus or larger reactions developed in 84 (20.0 percent); among 108 with 1 plus or negative reactions, supplementary intracutaneous tests with 1:500 *U. gracilis* extract produced 2 plus or larger reactions in 67 (62 percent). Nasal provocation tests were done extraseasonally in 16 subjects with late summer hay fever and 3- or 4-plus epidermal reactions to *U. gracilis* pollen; and, in 2 of these, the skin and mucosal response to nettle extracts definitely exceeded those to short ragweed pollen. No eye or bronchial challenge tests or leukocyte histamine release studies were described. Passive transfer and radioallergosorbent tests were not done.

Effectiveness for immunotherapy. No controlled studies were found on immunotherapy with nettle pollen extracts.

Recommendations. The Panel recommends that extracts of *Urtica* species pollens be placed in Category I for skin tests diagnosis and Category IIIA for immunotherapy.

b. *Parietaria. P. officinalis* (wall pellitory) is the prototype plant. It is widely distributed throughout the temperate regions of the world and in those European countries where it is abundant, it appears to be a serious cause of both hay fever and asthma. It pollinates from April to September or perennially (Refs. 43, 44, 85 through 88, and 90). Crifo et al. (Refs. 98 and 169) have attempted to separate the antigens of *P. officinalis* by discontinuous electrophoresis in polyacrylamide gel. They obtained 12 protein fractions which produced positive direct skin tests and passive transfer tests in 11 patients with pollinois caused by *P. officinalis* pollen. Serafini (Ref. 86) states that wall pellitory pollen does not cross-react with nettle pollen. The Panel found no other reports with reference to relationships and cross-reactions of antigens in wall pellitory pollens with those of other species of pollens.

Effectiveness for skin test diagnosis. Serafini (Ref. 86) reported that 944 patients clinically sensitive to wall pellitory pollen had positive skin tests with wall pellitory extract. Of these 944 patients, 529 were thought to be sensitive only to wall pellitory pollen. The incidence of asthma was noted to be unusually high, 67.5 percent, in these patients with wall pellitory pollinosis. One thousand two hundred and seventy-five patients with pollinosis had negative skin reactions to wall pellitory extract. No eye, nose, or bronchial challenge tests or leukocyte histamine-release tests were described. No passive transfer or radioallergosorbent tests were reported. The source of and manufacturing process for the wall pellitory extract were not described.

Panzani (Ref. 87) reported 12 patients with hay fever and asthma during the wall pellitory pollen season who were thought to be clinically sensative to wall pellitory pollen. All had positive cutaneous tests to wall pellitory pollen; six had skin reactions to no other pollen. No skin tests in nonallergic patients were reported.

Effectiveness for immunotherapy. No controlled studies were found on immonotherapy with wall pellitory extract. Uncontrolled studies suggest, but do not prove, that such immunotherapy may benefit some patients with asthma and hay fever due to wall pellitory pollinosis (Ref. 87).

Recommendations. The Panel recommends that extract of *Parietaria officinalis* pollen be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

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B. Allergenic Extracts of Mammalian and Avian Origin

1. *Definitions.* a. "Epidermal allergenic extract" means a preparation of an allergenic product obtained by extraction of the active constituents from the skin and/or its components and/or its appendages of animals, sometimes referred to as an "epithelial extract."

b. "Skin" means the continuous flexible integument forming the usual external covering of an animal body; it consists of the dermis and epidermis. "Skin" may also mean the integument of an animal stripped from the body, with or without the hair or feathers; referred to as "pelt" or "hide."

c. "Epidermis" means the outer, nonvascular layer of the skin of animals.

d. "Dander" or "dandruff" means the dead scarf-skin continuously separating from the epidermis in small scales, and entangled in the hairs.

e. "Hair" means the visible epidermal appendage of mammals.

f. "Fur" means the short fine hair of certain mammals which grows thick upon the skin and is distinguished from ordinary hair which is longer and coarser. "Fur" may also mean the processed skin of such animals used in making garments.

g. "Wool" means the unprocessed fine soft curly hair forming the fleecy coat of the domesticated sheep and similar animals. When prepared for making cloth, this hair is also called "wool."

h. "Feather" means the visible epidermal appendage of birds.

2. *Introduction*—a. *Clinical aspects of respiratory allergy to animals.* Respiratory allergy to nonhuman mammals, frequently referred to as epidermal allergy or animal dander allergy, has been recognized for more than 100 years. Almost any species of mammal with which humans come in contact may be the cause of animal dander allergy as is discussed most extensively in older textbooks on allergy. Allergens of mammalian origin (exclusive of foodstuffs) can induce inhalant allergies (usually regarded among the nonseasonal allergies and including allergic rhinitis, conjunctivitis, and asthma), urticaria, and anaphylaxis. That these allergies are mediated by specific IgE antibodies has been amply demonstrated. On this basis, confirmation of the diagnosis of specific allergy can be obtained, using extracts prepared from various mammalian sources, by: (1) immediate skin test reaction, (2) bronchial provocation test, (3) in vitro leukocyte histamine release test; (4) passive skin transfer test; and (5) radioimmunoassay.

Allergies to mammalian tissues are among the most common allergies, as noted by Berrens (Ref. 1). Feinberg (Ref. 2) stated that, in his series of allergic patients, 10 percent reacted to cat epidermal extract, 10 percent to dog epidermal extract, 8 percent to horse epidermal extract, 7 percent to cow epidermal extract, etc. In a series of 2,829 allergic patients, Rynes (Ref. 3) found a 10-percent incidence of cat sensitivity, a 10-percent dog sensitivity, an 8-percent horse sensitivity and a 7-percent cow sensitivity. Hannaway and Hyde (Ref. 4) found that positive skin tests to cat and dog epidermal extracts may be apparent during the first year of life. These figures must be regarded as approximations since in none of these studies were standardized allergens used nor was sensitivity to the allergens established by a standardized method.

Muljono and Voorhorst (Ref. 5) reported the results of skin tests with animal danger extracts done in 1,136 patients who visited the allergy clinic of the Leiden University Hospital for the first time in 1974 and 1975. The

frequencies of distinct skin reactions in the 1,136 patients were as follows: cat, 12.9 percent; guinea pig, 9.2 percent; horse, 6.3 percent; rabbit, 6.1 percent; golden hamster, 2.7 percent; cow, 2.6 percent; dog, 2.0 percent; pig, 1.8 percent; rat, 1.7 percent; and mouse, 0.6 percent. All the extracts used in these tests were said by the authors of this study to be standardized and to have been made "equivalent" (Ref. 6). Interestingly, about one and a half times as many females were found to be sensitive to animals as males; the proportion of females to males in the population tested was approximately equal. Regarding the frequency distribution according to age, allergy was found to occur most frequently in patients between ages 21 and 30 years, resembling grass pollen allergy in this respect.

Muljono and Voorhorst (Ref. 5) also analyzed the type of allergic complaints and the relationship between the intensity of skin reactions and complaints according to exposure in their dander-sensitive patients. Regardless of the animal involved, the highest frequency of positive reactions to dander extract occurred in patients with asthma (possibly combined with rhinitis); the next highest frequency occurred in patients with atopic exzema. Patients who had a definitely positive skin reaction to one or more dander extracts were questioned about the occurrence of allergic symptoms (itching, nasal and eye complaints, and dyspnea) after contact with animals, and their decrease after discontinuance of contact. Comparison of the magnitude of the skin tests with case histories revealed that patients with a low degree of skin sensitivity were unlikely (about one chance in six) to have allergic complaints after contact with the relevant animal. In contrast, patients with strong skin test reactions had a high probability (about four out of five) of having clinical complaints after contact. An almost identical relationship was found for grass pollen-sensitive patients in their clinic.

The above-noted data notwithstanding, the full extent of the problem of allergy to mammals, i.e., the number of individuals sensitive to animals and the number at risk, is not known. Some indication of the incidence of animal dander allergy is revealed in recent surveys of allergy to laboratory animals. Lutsky and Neuman (Ref. 7) reported that 14.7 percent (191) of 1,293 individuals with direct daily contact with laboratory animals in 39 different facilities reported symptoms of animal dander allergy. Lincoln et al. (Ref. 8) found that 11.3 percent (27) of 238 individuals with significant exposure to laboratory animals in a single reasearch facility had one or another type of hypersensitivity reaction. The frequency of animal dander allergy in the general population is probably lower than this since laboratory workers often have more intense exposure to animals than most people.

Animal dander allergy is a significant occupational disease among veterinarians and animal handlers, research scientists and laboratory technicians. Lutsky and Neuman (Ref. 7) reported that 28 percent of the allergic individuals in their survey either had to decrease their contact with animals or change jobs. The remaining 72 percent were able to continue their work by using a mask and/or medication. Lincoln et al. (Ref. 8) reported that symptoms were sufficiently severe in 10 of 27 research workers that they had to modify their research or delegate their work to others. These authors went so far as to recommend that individuals with a history of any allergy should not be employed in areas where they might have frequent contact with animals.

Among persons with allergy to laboratory animals, typical symptoms are reported to begin within 5 to 10 minutes after exposure. Multiple respiratory symptoms are common. For example, in Lutsky and Neuman's survey (Ref. 7), 100 percent of the subjects had rhinitis with conjunctival symptoms; 71 percent reported asthma; 58 percent reported cough; and 38 percent reported palatal itch. Allergic manifestations of the skin (principally localized urticaria) were reported by 58 percent of the subjects. In Lincoln's study (Ref. 8), 22 of 27 allergic subjects had nasal and/or conjunctival symptoms when in contact with animals; 13 had episodes of asthma, sufficiently severe in 5 to require regular bronchodilator therapy. For reasons as yet unknown, asthma seems to occur more frequently in animal dander allergy than in pollen allergy. Other manifestations of animal dander allergy are angioedema, eczema, and systemic anaphylaxis (following an animal bite). Allergenic individuals may incur a local wheal and erythema reaction when they are scratched or when they have contact with the hair of the animal to which they are allergic; some individuals report the same symptom when the animal's urine, blood, saliva, or sweat touches their skin.

Individuals with animal dander allergy are frequently (55 percent in one series—Ref. 7) sensitive to more than one animal, and it is sometimes difficult to determine by clincial evidence alone which species is responsible for the allergic symptoms. To what extent this may be due to the existence of cross-reacting allergens in different animal species is not known; there is some evidence for this possibility (Refs. 9, 10 and 11). Symptoms attributable to animal dander allergy may be aggravated during a period of seasonal allergy; and some individuals report that their pollen allergies are made worse by frequent exposure to animals to which they are allergic (Ref. 8).

The natural history of animal dander allergy is poorly documented. Rackemann and Edwards (Ref. 12) analyzed retrospectively the outcome of animal dander allergy in one group of asthmatic children first seen by them before age 13 years and in another group who were not seen until age 13 years or older. Seventeen percent of the first group of 114 children had lost their sensitivity, manifested principally as asthma to cats, dogs and/or horses when seen 20 years later. Some of these patients may have been helped by separation from the animal or by injection therapy. Nearly half the group was clinically well, but was still sensitive to one or more animals, i.e., contact with animals still caused asthma. Eleven percent of these patients reported persistent mild asthma, although it was not always induced by contact with animals. Six percent still suffered from allergy to animals, which had begun at an average age of 2½ years. Fifteen percent of the children had lost their early asthma as well as their sensitivity to animals, but later suffered recurrent allergic symptoms, usually pollen-induced hay fever. Among 239 children with asthma who were not seen until age 13 years or older (the second group), 32 percent (76) were allergic to animals. Patients in this older age group did not fare as well as those in the younger group; only about half were clinically well when seen 20 years later.

b. *The allergens.* The principal source of mammalian allergens is generally considered to be dander, the epithelial debris which may become airborne after being shed. In constrast to the vast literature on airborne allergens from plant sources, there is only limited information about airborne dander. Clark et al. (Ref. 13) reported that the bulk of airborne particles in the home consists of dander, most likely of human origin; these particles are in the size range 0.3 to 0.4 micrometers in diameter Ref. 14). The load of airborne dander derived from domestic animals in the home has not been estimated.

The total dust concentration in laboratory animal rooms is a function of the density of the animal population. For example, the total dust load in a mouse room with 800 cages of mice was reported to be 0.05 mg/m³ of air; in a mouse room with 475 cages, it was 0.037 mg/m³ of air; and in a hallway outside the animal room, it was 0.016 mg/m³ of air (Ref. 8). However, the quantity of specific allergen in these airborne particles was not determined.

In rooms housing laboratory mice, animal dander particles were reported to range in size from 4 to 41 micrometers in diameter (Ref. 8). Most were in the 12 to 20 micrometer diameter range; less than 3 percent were in the range below 7 micrometers. Particles 2 micrometers in diameter or less, of particular interest because they are most likely to be deposited in the lower respiratory tract when inhaled (Ref. 15), were not observed by Lincoln et al. (Ref. 8); however, this may have been due to their sampling and assay methods.

Dander is not the only source of mammalian allergens. Spain et al. (Ref. 16) showed by skin test reactions that extracts of dog, cat, or rabbit saliva contain allergenic material. Animal hair is obviously contaminated with saliva, due to the animal's grooming habits. Thus a small amount of salivary protein is probably present in most epithelial extracts. Spain et al. believed that salivary as well as epithelial allergens are responsible for clinical sensitivity. Recently, Karpas and Baer (Ref. 17) reported that cat pelt extract contained no allergens not found in cat salivary extract or in serum, implying that there is no unique allergen in the epithelium. Guerin and Hewitt have made a similar observation (Ref. 18) and suggested that saliva might be a suitable source material for allergenic extracts.

Urine was recetly reported to be a major source of allergenic protein in mice and rats (Ref. 19). Urinary allergens may be identical to those present in saliva or serum (Ref. 17). It is not surprising that airborne particles in animal rooms contain urinary proteins as well as dander proteins (Ref. 8).

Serum has long been recognized as a major source of mammalian allergen (Ref. 20). Squire (Ref. 21) obtained evidence that albumin in horse dander extract is identical to serum albumin and that both are allergenic. Stanworth (Ref. 22), using immunoprecipitation, found that small quantities of serum albumin and globulin are present in horse dander extract. Yman et al. (Ref. 23) and Ponterius et al. (Ref. 24), using polyacrylamide gel electrophoresis combined with immunodiffusion and the radioallergosorbent test also reported that serum albumin is an important allergen in horse epithelial extract whereas it was present to only a minor degree in horse dander extract. This study made the important point that the composition of a mammalian extract depends heavily on the source materials used in its preparation, whether they be hair, dander, epithelia or whole dermis. An extract of hair might contain components originating from the environment, e.g., pollen, while an extract of whole pelt will contain a large proportion of serum proteins. For example, mouse serum albumin was found to comprise about 50 percent of the protein in mouse skin extract (Ref. 25). Other serum proteins are present to a lesser extent; and some of these may be allergenic (Ref. 26). Several investigations (Refs. 9, 24 and 27) have documented the fact that a minority of people with animal dander allergy are allergic to an allergen found principally in serum; of this minority, many are probably sensitive to allergens from both dander and serum.

A number of commercial allergenic extracts are still made from animal hair or fur although it is now recognized that hair, per se, does not contain these allergens (Refs. 1 and 23).

Feinberg (Ref. 2) stated that furs, i.e., skins which have been treated, cleaned and sterilized, are not a source of allergenic material. Processed furs may cause contact dematitis due to dyes and finishing materials rather than to epithelial allergens. However, trappers and furriers who are in contact with unprocessed skin may become allergic to them.

Ohman et al. (Ref. 10) studied the distribution of allergenic activity in various cat tissues using a RAST inhibition technique and found that an extract of cat brain contained significant allergenic activity; activity was also detected in an extract of parotid gland but not in extracts from 10 other major organs.

Levy (Ref. 25) sought, but did not find, allergenic activity in highly purified mouse histocompatibility antigens.

Extracts prepared from different breeds of the same animal species are available commercially. It is still questionable whether allergy may exist to one breed and not to another of the same species. On the basis of cross-neutralization experiments, Hooker believed that it could (Ref. 28). Fagerberg and Wide (Ref. 29) found evidence for breed-specific allergenic determinants in dogs; so did Varga and Ceska (Ref. 30). However, these findings can probably be ascribed to quantitative rather than qualitative differences in the components of extracts prepared from different breeds. Recently, Blands et al. (Ref. 31) analyzed extracts prepared from the dandruff of six different dog breeds by the powerful techniques of crossed radioimmunoelectrophoresis (CRIE) and quantitative immunoelectrophoresis (QIE) and found both quantitative and qualitative differences between the individual dog breeds but no breed-specific allergens were identified in extracts from individual dog breeds. Therefore, until additional studies have been done, the question must remain unanswered.

The general subject of allergen chemistry, including allergens of mammalian origin, has been reviewed by Berrens (Ref. 1), Stanworth (Ref. 32), Spies (Ref. 33) and Marsh (Ref. 34). Recently published methods for the isolation and characterization of allergenic extracts from animal sources should be particularly useful in future work on these materials (Ref. 35). For example, Ohman and his colleagues (Refs. 10 and 36) have suggested that the major allergen of cat pelt which they have isolated may be used to standardize cat epidermal extracts in the same way that antigen E is being used to standardize whole ragweed extracts. To date, allergenic extracts from mammalian sources are not available as standardized preparations.

3. *General review and recommendations.* The following are category recommendations for those extracts prepared from mammalian and avian sources as listed by the manufacturers in their data submissions, BER Volumes 4001 through 4026:

CATEGORY RECOMMENDATIONS FOR ALLERGENIC EXTRACTS OF MAMMALIAN AND AVIAN ORIGIN

Extract	Diagnosis	Immunotherapy
Angora goat/mohair	IIIA	IIIA
Angora wool, rabbit and antelope hair mix.	IIIB	IIIB
Beaver	IIIA	IIIA
Beaver fur	IIIB	IIIB
Camel	IIIA	IIIA
Camel hair	IIIA	IIIA
Caracul fur	IIIB	IIIB
Cashmere	IIIA	IIIA
Cat	I	IIIA
Cat dander	I	IIIA
Cat hair	I	IIIA
Cat hair and dander	I	IIIA
Cattle	IIIA	IIIA
Cattle dander	IIIA	IIIA
Cattle hair	IIIA	IIIA
Cattle hair and dander	IIIA	IIIA
Chamois skin	IIIB	IIIB
Chihuahua	IIIA	IIIA
Chinchilla	IIIA	IIIA
Chinchilla Fur	IIIB	IIIB
Cow	IIIA	IIIA
Cow dander	IIIA	IIIA
Deer dander	IIIA	IIIA
Deer hair	IIIA	IIIA
Dog	I	IIIA
Dog dander	I	IIIA
Dog hair	I	IIIA

CATEGORY RECOMMENDATIONS FOR ALLERGENIC EXTRACTS OF MAMMALIAN AND AVIAN ORIGIN—Continued

Extract	Diagnosis	Immunotherapy
Dog hair and dander (mixed breeds).	I	IIIA
Elk hair	IIIA	IIIA
Ermine fur	IIIB	IIIB
Feathers, canary	IIIA	IIIA
Feather, lint, mixed	IIIA	IIIA
Feather, mix (chicken, goose, duck).	IIIA	IIIA
Feathers, chicken	IIIA	IIIA
Feathers, duck	IIIA	IIIA
Feathers, goose	IIIA	IIIA
Feathers, mixed	IIIA	IIIA
Feathers, parakeet	IIIA	IIIA
Feathers, parakeet-parrot	IIIA	IIIA
Feathers, pigeon	IIIA	IIIA
Feathers, turkey	IIIA	IIIA
Fox fur	IIIB	IIIB
Fox, red	IIIA	IIIA
Fox, silver	IIIA	IIIA
Fur mix	IIIB	IIIB
Gerbil	IIIA	IIIA
Gerbil fur	IIIB	IIIB
Goat	IIIA	IIIA
Goat dander	IIIA	IIIA
Goat hair	IIIA	IIIA
Goat hair (angora)	IIIA	IIIA
Goat hair (dairy)	IIIA	IIIA
Goat hair and dander	IIIA	IIIA
Goat hair (milk)	IIIA	IIIA
Guinea pig	IIIA	IIIA
Guinea pig hair	IIIA	IIIA
Hamster	IIIA	IIIA
Hamster hair	IIIA	IIIA
Hog	IIIA	IIIA
Hog dander	IIIA	IIIA
Hog Hair	IIIA	IIIA
Hog hair and dander	IIIA	IIIA
Horse	I	IIIA
Horse dander	I	IIIA
Horse hair	I	IIIA
Horse hair and dander	I	IIIA
Human dander	IIIA	IIIA
Human hair	IIIA	IIIA
Kolinsky fur	IIIB	IIIB
Lamb, black	IIIB	IIIB
Leathers	IIIA	IIIA
Leather, cow and horse	IIIA	IIIA
Leopard	IIIA	IIIA
Leopard fur	IIIB	IIIB
Marmot fur	IIIB	IIIB
Mink	IIIA	IIIA
Mink fur	IIIB	IIIB
Mohair	IIIA	IIIA
Mole fur	IIIB	IIIB
Monkey	IIIA	IIIA
Monkey dander	IIIA	IIIA
Monkey hair	IIIA	IIIA
Mouse	IIIA	IIIA
Mouse hair	IIIA	IIIA
Muskrat	IIIA	IIIA
Muskrat fur	IIIB	IIIB
Muskrat fur (Hudson seal)	IIIB	IIIB
Nutria fur	IIIB	IIIB
Opossum fur	IIIB	IIIB
Persian lamb fur	IIIB	IIIB
Pony	IIIA	IIIA
Pony fur	IIIB	IIIB
Poodle, French	IIIA	IIIA
Poodle hair	IIIA	IIIA
Rabbit	IIIA	IIIA
Rabbit dander	IIIA	IIIA
Rabbit hair (fur)	IIIB	IIIB
Racoon	IIIA	IIIA
Racoon fur	IIIB	IIIB
Rat	IIIA	IIIA
Rat hair	IIIA	IIIA
Sable fur	IIIB	IIIB
Seal fur, Alaskan	IIIB	IIIB
Seal fur	IIIB	IIIB
Sheep wool	IIIB	IIIB
Skunk	IIIA	IIIA
Skunk fur	IIIA	IIIA
Squirrel	IIIA	IIIA
Squirrel fur	IIIB	IIIB

Perusal of this list that some extracts are prepared from sources which are ambiguously identified: e.g., "feather, lint, mixed;" "fur mix;" "leathers." Separate extracts are prepared from raw materials obtained from horse and from pony, obviously animals of the same species. Materials from the same species are also identified as from separate sources in another way, viz., cattle and cow. In many cases, the specific source material itself, e.g., dander or hair, is not identified; in other cases, only the species, viz., beaver, camel, etc., is identified. In no case is the scientific name of the animal source used to identify the extract.

These so-called epidermal extracts are prepared from a variety of source materials, including whole pelt, shaved pelt or hide, hair, processed fur, feathers, and material obtained by clipping, shaving, brushing or vacuuming the animal or its pelt. Criteria for determining the identify and purity of these source materials are nowhere specified by the manufacturers. In most cases, the suppliers of the source materials are not identified.

Berrens (Reft. 37) found considerable variation in the percentage of dry dander obtainable from the hair of seven different animal species as well as a 10-fold difference in the amount of high-molecular-weight material extractable from these source materials. In that study, the highest proportion of soluable material was obtained from the dander of dog, horse, cat, and rabbits; the yield from mouse dander was extremely low.

Guerin and Hewitt (Ref. 38) recently found that extracts prepared from non-defatted and acetone-defatted cat fur were similar in composition.

Extraction methods used in the manufacture of epidermal extracts are generally similar to those used to manufacture allergenic extracts from other sources, i.e., simple suspension of the source material in a buffered salt solution. Some manufacturers concentrate their extracts by precipitation with a salt or an organic solvent. Guerin and Hewitt (Ref. 39) report that alkaline-pyridine extraction of cat fur reduces the allergenic activity markedly compared to extraction with Coca's solution or with glycero-saline solution.

Current Federal regulations stipulate that source materials used in the manufacture of allergenic products "shall be free from blood and serum" (Ref. 40). While it should be relatively easy to determine the amount of specific animal serum proteins, e.g., albumin, that are present in these extracts, this is not currently being done. The potential hazard of the serum proteins in epidermal extracts has not been studied.

The manufacturers submitted no data on the stability of their epidermal extracts. Regarding short-term stability, early evidence indicated that horse dander extract could withstand heat for 1 hour at 100° C when at pH 7.4 or 9.0, but it was rapidly inactivated when heated at pH 4.5 (Ref. 41). In contrast, however, Squire (Ref. 21) reported that horse dander extract withstood boiling only for a few seconds; activity was lost after 30 minutes at 100° C. Boiling at pH 5 to 6 produced a jellylike coagulum. Autoclaving destroyed 99 percent of the activity. Acidity alone does not inactivate epithelial allergens, since material reactive in vitro with IgE antibody can be eluted from polyacrylamide gels at pH 4.2 (Ref. 30). Varga and Ceska (Ref. 30) found significant changes in the isoelectrofocusing pattern of a commercial dog extract after 10 months storage at 4° C. Inactivation of epidermal allergens during storage might be due to the presence of proteolytic enzymes. The Panel found no other report on the long-term stability of epidermal extracts.

Epidermal extracts are generally regarded as safe for use in diagnosis and therapy of specific allergies although, as with other allergens, constitutional reactions have been induced in highly sensitive patients. The Panel found no reports in which the short-term and long-term safety of this class of extracts, as used in diagnosis and therapy, had been studied.

The Panel considered the likelihood that some infectious agents might be transmitted to patients receiving epithelial extracts. In the opinion of several virologists (Refs. 42 and 43) viral contamination of animal epithelial tissues (but not hair) is theoretically possible, but the likelihood of transmitting such viruses to human recipients is very small indeed. Hardy tested 8 lyophilized commercial cat dander extracts for feline leukemia virus (FeLV) (Ref. 44). Using a fluorescence technique, none of the extracts was found to contain FeLV antigen. The likelihood of regular contamination with a detectable amount of virus is so small that it was not regarded by the Panel as being worth the effort to search further.

Most manufacturers make no consistent effort to ascertain the health of the animals from which the source materials are obtained. Because these allergenic products are used in humans, the Panel supported the requirement of the National Center for Drugs and Biologics that the animals from which the source materials were obtained

should be in good health at the time they were obtained.

In summary, allergy to animals is a well-documented clinical entity, and commercially available extracts are generally accepted as being an aid in its diagnosis.

In contrast, the Panel found few reports on the therapeutic effectiveness of epidermal extracts, and those found could not be regarded as being adequate clinical trials. For example, Rynes (Ref. 3) reviewed the results of therapy with several animal dander extracts (including cat, dog, horse, and rabbit) in 235 patients treated in an asthma clinic. The study group was not described. The results of therapy were not analyzed according to the specific extract administered. Patients were advised to eliminate all possible contact with animals responsible for positive skin tests, but patient compliance with this recommendation was not reported. The dosage and course of treatment were not given. Retrospectively, 46 percent of the patients reported a good result; 41 percent, a fair result; and 13 percent, a poor result; criteria for judging these results were not described. The author nevertheless concluded that immunotherapy is a feasible and satisfactory method of treatment when avoidance of the animal is not possible.

Virtually nothing is known about immunological changes which may acccompany therapy with these extracts.

It is evident from the above discussion and from comments in the subsequent statements on individual epidermal extracts that there is a gross lack of information on the methods of preparation and use of these extracts.

One of the most important unanswered questions concerns the effectiveness of immunotherapy with epidermal extracts. Although several extracts are widely used in practice (viz., cat and dog extracts), most authorities still recommend avoidance of contract as the best therapeutic measure (Ref. 45).

A number of changes for extracts of animal and avian origin were recommended by the Panel. The first of these is the inclusion of more accurate descriptions of source materials in labeling which should be met within a year. Other goals, e.g., establishment of reference preparations, use of standards to assure consistent and potent products and determination of safety and effectiveness in diagnosis should be met within 5 years. Studies of safety and effectiveness for use in therapy must then begin for those extracts for which Category IIIA is recommended by the Panel. To achieve Category I status for therapy, a period of 10 years is suggested as the limit.

4. *The most commonly used epidermal extracts*—a. *Cat (Felix Domesticus)*—(1) *General description.* All cats are members of the family *Felidae.* The house cat has been domesticated since about 1500 B.C. Domestic cats in the United States date from around 1750. There is a moderate number of distinctive breeds of cats, differing mainly in color and texture of the coat. The basic classification is into long-haired and short-haired varieties. Domestic cats, like dogs, are of increasing economic importance in this country on account of their numbers and the money spent on their care. Cats are not bred for economic purposes, although some are used in biomedical research (Ref. 46).

(2) *Clinical aspects.* "Cats are by far the most highly allergenic animals encountered by most people," according to Gutman (Ref. 47). The entire spectrum of respiratory allergies, as well as urticaria, occurs in persons allergic to cats. In various studies of animal dander allergy, the incidence of positive skin tests to cat epidermal extracts in groups of allergic subjects ranged from 9 to 32 percent (Ref. 1). This included Rynes' study (Ref. 3) of 2,682 allergic patients, with 9 percent reacting to cat dander extract. He found that young patients (those less than 20 years of age) predominated among cat-sensitive patients. Additional descriptions of clinical aspects of allergy to cats can be found in textbooks of allergy (see, for example, Ref. 2).

(3) *Product description.* This product is available as cat, cat epidermal, cat epithelial, cat dander, and cat hair extracts; an extract prepared from source material obtained from Siamese cats is also available. Both aqueous and glycerinated extracts are marketed, either as weight per volume or PNU solutions.

The source materials for the manufacture of cat epidermal extracts are eigher pelt or hair and dander removed from pelts. The origin of these source materials is identified by some manufacturers, not by others, in information submitted to the Panel.

Methods used in the manufacture of cat epidermal extracts are those generally used in the preparation of other epidermal extracts. The Panel found the following descriptions of the preparation of cat epidermal extracts.

Holford-Strevens (Ref. 48) obtained skin from cats used in laboratory research. Skin was used as the source of allergen since it was more easily obtained in quantity than dander and it yielded extracts that were more potent in skin tests than commercial cat dander extracts. The skin was minced, defatted with ether, extracted in Coca's solution for 7 days, Seitz filtered, dialyzed, and then lyophilized. Variations in the pattern of response to fractions of cat skin extract among a group of cat-sensitive patients suggested the presence of multiple allergens. Skin tests were also done with serum because skin extract was presumed to contain serum proteins. In general, skin extract was more potent than cat serum; only 5 of 22 cat-sensitive patients reacted to this serum, whereas all of them reacted to the skin extract.

Ohman et al. (Ref. 9) prepared cat pelt extract as follows: fresh, unshaved cat pelts were washed with water, then lyophilized. Lyophilized pelts were defatted with ether, thoroughly dried and extracted with water (1:10 w/v) at room temperature for 6 hours and then overnight at 5 °C. After neutralization, the aqueous extract was filtered through cotton gauze, then through Millipore filters (to a final pore size of 0.22 microns). Aliquots were lyophilized and stored under sterile conditions at 5 °C. Thirteen subjects clinically sensitive to cats reacted equally to this extract and a commercial extract of cat hair. The yield of allergen from a single pelt was said to be much greater than could be obtained from the hair and dander of a single cat.

Recently, Guerin and Hewitt (Ref. 38) showed that defatting of cat fur (obtained by shaving a live cat close to the skin with an electric clipper, then chopping the shavings with scissors) with acetone prior to extraction produced no major difference in the final extract compared to a non-defatted extract of the same fur. They did find significant differences between cat fur extracts prepared with Coca's solution, glycero-saline solution and alkaline-pyridine solution (Ref. 39). Indirect RAST with sera from 33 cat-sensitive patients, the pyridine-extracted material gave significantly lower values in all instances except one. On isoelectricfocussing gels, the pyridinated extract gave protein bands in the pH 5.0 to 7.0 region, whereas the other two extracts gave bands in the pH 3.0 to 5.0 region. With one serum, the analytical isoelectricfocussing pattern of the pyridinated extract presented allergenic activity throughout the pH range of 3 to 7 and was more-or-less comparable to patterns obtained with the other preparations. In all other instances, however, there was little activity in the pyridinated extract, whereas the other two preparations were comparable in the level of activity although their

patterns were not identical. The data suggest that (1) alkaline-pyridine extraction alters cat epidermal allergens to a significant degree; and (2) the same extraction procedure should be used for both diagnostic and therapeutic extracts in order to make them equivalent.

Guerin and Hewitt (Ref. 18) prepared extracts of cat fur, pelt, and saliva and tested them by RAST, RAST inhibition, and isoelectricfocussing. They found some differences in allergenic composition by RAST inhibition using a pool of serum from cat-sensitive donors and by titrating fractionated extracts against individual sera, although the majority of the allergenic components of each extract appeared to be common to all three sources.

(4) *Composition.* Considerable progress has been made in recent years in the characterization of allergens from cat skins by Varga and Ceska (Ref. 30), Brandt et al. (Ref. 27), Holford-Strevens (Ref. 48) and Ohman et al. (Refs. 9, 10 and 36). According to Ohman, the allegenic activity of pelt extract is present in proteins with prealbumin, albumin and alpha-2 globulin mobilities; the molecular weights of these proteins fall in the range 30,000 to 60,000 daltons. A protein fraction (obtained from DE52 cellulose and Sephadex gel columns) with prealbumin mobility was resolved into four protein bands on electrophoresis in 10 percent polyacrylamide gel. The band with the bulk of the allergenic acticity (as determined by skin test) was designated "cat allergen 1." Rabbit antibody to this protein was able to remove most of the allergenic activity from crude cat pelt extract, thus supporting Ohman's claim that cat allergen 1 is the major allergen in cat pelt.

However, there is considerable evidence that there is at least one additional cat allergen which is present in serum as well as in epidermal extracts. Wodehouse (Ref. 49) long ago found that of 8 patients who had positive skin reactions to cat dander extract, 5 also reacted to cat serum. Brandt et al. (Ref. 27) tested sera from 56 cat-sensitive patients with a RAST assay and found that 37 reacted with epithelial allergen, 4 reacted with serum allergen alone and 15 reacted to both. Nevertheless, Ohman et al. (Ref. 9) reported that about half of his patients who reacted to cat pelt extract in skin tests also reacted to cat serum. Ohman (Ref. 36) believes that albumin is not a major cat allergen, that is, a majority of cat-sensitive individuals are not allergic to cat albumin. In contrasts to studies of epidermal allergens from other species, he found allergenic activity not in albumin but in a protein fraction of cat serum having a molecular weight between that of albumin and gamma-globulin. He did not, however, indentify this allergen. With a RAST technique, Ohman et al. (Ref. 36) found evidence of common allergens in cat and dog sera. This finding has not been confirmed, and its clinical significance remains obscure. It is not known whether these allergens are present in the environment in sufficient amounts to cause symptoms in individuals actually allergic to one or the other of these animals.

As pointed out above, Karpas and Baer (Ref. 17) recently reported that lyophilized cat pelt extracts appear to contain allergens from cat serum, saliva, and urine. Two lots of extract which they examined reacted somewhat differently in RAST, possibly because of dissimilar content of allergens. They suggest that the allergens in pelt extract are actually derived from serum and saliva. Moreover, they believe that pelt and urine may not contain unique allergens. Spain et al. (Ref. 16) had, as previously noted, found a common allergenic factor in skin and salivary extracts from cats, and this was recently confirmed by Guerin and Hewitt (Ref. 18).

Voorhorst (Ref. 50) studied extracts prepared from several breeds of cats, including so-called "common" cats. Four subjects were tested with varying dilutions of "common" cat extract and a Siamese cat extract. One subject reacted to common cat and minimally to Siamese cat, whereas the other three subjects reacted to Siamese cat but not to "common" cat extract indicating that Siamese cat extract does contain a strain-specific allergen, not common to other cats. Still, after testing 5 patients with extracts prepared from the dander of 6 different cat breeds, he stated that some of these differences in the skin test response to different breeds were probably due to quantitative, not qualitative, differences between these extracts. However, as noted by Berrens (Ref. 1), inadequate knowledge of the quantity of individual allergens in extracts prepared from various breeds may well lead to erroneous conclusions.

(5) *Standardization.* There is no established standard of potency for this product. No comparison is made by the manufacturers of skin reactions produced by any particular batch or lot with reactions produced by a reference batch. No information was provided by the manufacturers on the reproducibility of skin reactions with different lots of this extract, nor was information provided on the determination of potency by in vitro techniques. No information was provided on the stability of this product.

Using RAST, Varga and Ceska (Ref. 30) found that the allergen content of commercial cat dander extracts produced by several firms differed by as much as 1,000 fold. Furthermore, there was no correlation between the total protein concentration and the allergen content of these extracts. Nevertheless, despite differences in potency, the isoelectricfocussing patterns of the extracts were similar, suggesting that the differences were, in fact, mainly quantitative.

Brandt et al. (Ref. 27) studied two cat epithelial extracts: one was a commercial extract from Eurpoean short-haired cats; the other was prepared from scraping of a dried European short-haired cat hide. Using the RAST assay of Ceska et al. (Ref. 51), they found that the concentration of epithelial allergens differed in the two extracts by approximately 100-fold. The two extracts did contain comparable amounts of "allergens originating in serum."

Ohman et al. (Ref. 36) found considerable variation in the allergen content of eight commercial cat epithelial extracts. All of these extracts, as well as an extract prepared by Ohman from Siamese cat pelt, contained different amounts of allergenic activity as determined by prick tests in 10 randomly selected cat-sensitive individuals. Allergenic activity correlated strongly with activity determined by RAST assay for cat allergen 1, the principal allergenic component identified by Ohman et al. The results of both of these tests also correlated well with cat allergen 1 content determined by immunodiffusion assay. The content of cat allergen 1 in the eight commerical extracts ranged from 1 to 25 micrograms/milliliter; it was 33 and 14 micrograms/milliliter in the mongrel and Siamese cat pelt extracts, respectively. Cat serum albumin content of these extracts was measured by immunodiffusion assay and found to range from 1 to 28 micrograms/milliliter. There was no correlation between the intensity prick test reactions to crude cat pelt extract and serum albumin content as determined by RAST assay. Total nondialyzable solids in the extracts ranged from 80 to 5,260 micrograms/milliliter. There was no correlation between the concentrations of cat allergen 1, albumin and total nondialyzable solids in any of the eight extracts. This study as well as others cited above highlight the significant differences that exist between the

currently available unstandardized commercial cat epidermal allergenic products. It also suggests that, as is the case with whole ragweed extract, a single allergenic component might be useful in estimating the potency of cat epidermal extracts.

(6) *Labeling.* Refer to the general statement on labeling and to comments in the product decription above.

(7) *Safety.* No information was provided by the manufacturers on the safety of cat epidermal extracts. Refer to comments in the product description above regarding the possible contamination of cat epidermal extracts with oncogenic viruses and serum proteins. Also refer to the general statement on safety.

(8) *Effectiveness*—(i) *For diagonsis.* Virtually no data were provided by the manufacturers on the effectiveness of their extracts for the diagnosis of allergy to cats. Nevertheless, the medical literature contains abundant evidence showing that immediate skin test reactions are induced by cat epidermal extracts in most clinically sensitive individuals. However, it is important to note that Rynes (Ref. 3) found that only 18 percent of a group of patients with a positive skin test to cat epidermal extract related contact with a cat to aggrevation of their allergic symptoms. Sarsfield et al. (Ref. 52) regard the clinical history to be a more reliable guide than skin tests in the diagnosis of clinically significant allergy to cats. That is to say, a positive skin test is often seen in children who have a cat but whose symptoms are not aggravated by contact with the cat. Such patients will usually have a negative RAST for cat-specific IgE antibody. In contrast, Curran and Goldman (Ref. 53) reported finding no positive reactions in 100 nonallergic individuals skin tested with 1,000 PNU of cat dander extact, and Fontana et al. (Ref. 54) observed a positive skin test to 1,000 PNU of cat dander extract in only 1 out of 100 nonallergic children. Thus, it would seem that false-positive skin test with cat epidermal extracts are not uncommon in otherwise allergic patients, while such reactions are probably uncommon in nonallergic individuals.

(ii) *Effectiveness for therapy.* No data were provided by the manufacturers demonstrating the effectiveness of cat epidermal extract for the treatment of allergy to cats. Although there has been no controlled clinical investigation of the therapeutic effectiveness of this extract, a few reports suggest that it may be effective in some patients.

Tuft and Torsney (Ref. 55) treated 18 cat-sensitive patients with alum-precipitated pyridine extract of cat pelt. There were 7 female and 11 male patients, ranging in age from 8 to 57 years. They had typical symptoms, including urticaria. Skin test reactions to aqueous cat pelt extract were positive in 10 and doubtful or sligthly positive in 8; the test does was not reported. Injections were given at 2-week intervals. There were no constitutional reactions, but there were 31 slight or moderate local reactions in 416 injections (7.5 percent). Fourteen of the patients (78 percent) reported a significant increase in tolerance to cats after treatment; this was not evaluated objectively. Immunological parameters were not measured.

Brown and Wolfe (Ref. 56) treated 27 cat-sensitive individuals with alum-precipitated pyridine-extracted cat pelt extract. Five reported definite improvement; 4 reported partial improvement; 18 reported no improvement. Seven cat-sensitive individuals were treated with aqueous cat pelt extract. Of these, one reported definite improvement; one, partial improvement; and five, no improvement.

Taylor et al. (Ref. 57) recently reported that bronchial sensitivity to cat pelt extract was reduced in a small group of cat-sensitive patients who received a course of immunotherapy with aqueous cat pelt extract. The report contained no data on clinical or immunological changes which may have resulted from this therapy.

(9) *Critique and conclusions.* The manufacturers provided no reliable data on the effectiveness and safety of their cat epidermal extracts for use in diagnosis and therapy.

Cat pelt appears to be an excellent source material for the manufacture of cat epithelial extract. Cat hair alone yields significantly less allergenic activity. The major allergen in cat epidermal extracts may be derived from saliva, a material which has been suggested as a suitable source material for extracts. Cat pelt extracts also probably contain serum proteins, among which there may be one or more minor allergens.

Breed-specific allergens appear unlikely. However, there may be quantitative differences in the content of given allergenic components in the pelts of cats of different breeds. Also, extraction of allergenic components from pelts of cats of different breeds may result in quantitatively different products. The present evidence suggests that mongrel cat pelts are an excellent source material.

Commercial cat epidermal extracts vary significantly in potency. To what extent this may be due to differences in manufacturing (including source material, preparation and storage of source material, extraction procedures, etc.) has not been determined. Currently, there is no reference standard or standard of potency for cat epidermal extracts. Skin testing, RAST inhibition, and measurement of the concentration of cat allergen 1 by immunoassay in gel are methods which might be used to standardize these extracts. Lyophilized cat pelt extract or purified cat allergen 1 may be satisfactory reference standards, if currently available evidence is confirmed by additional data.

There are several allergens in cat epidermal extracts to which sensitized individuals may react; cat allergen 1 appears to be the major one. The significance of minor allergens requires further investigation, as does the possible significance of allergens which cross react with those of other species, e.g., dog.

The true frequency of clinically significant allergy to cats in the general population is not known, but it is probably the most common epidermal allergy. The available data suggest that cat epidermal extracts may elicit positive skin tests rather frequently in individuals who are allergic, but who are not allergic to cats, while positive reactions in nonallergic individuals occur infrequently.

As yet, there has been no controlled clinical trial of specific therapy in cat-sensitive patients. In fact, methods for evaluating the clinical response to therapy have not been established. The results of several uncontrolled studies of this therapy are inconclusive, although a recent study suggests a definite benefit. Another recent report suggests that alkaline-pyridine extraction significantly reduces the allergenic activity of cat epidermal extract (Ref. 39). If this is the case, then conclusions drawn from therapeutic trials with this particular product are open to question. None of these studies included data on immunological parameters.

In conclusion, the Panel believes that there is sufficient evidence to state that cat epidermal extract, properly manufactured and standardized against an accepted reference preparation, will be an effective aid in the diagnosis of allergy to cats. The therapeutic effectiveness and safety of cat epidermal extract have not been established and require an objective, well-controlled clinical trial with appropriate immunologic studies.

(10) *Recommendations.* It is recommended that aqueous cat epidermal extract be placed in Category

I for skin test diagnosis and Category IIIA for immunotherapy.

b. *Dog (Canis domesticus)*—(1) *General description.* The domestic dog of the present day is descended from several canine species. Hooker (Ref. 28), citing Gwatkin, lists the following four ancient strains as the source of *Canis domesticus*: (a) An Egyptian jackal-like dog (*C. palustris*); (b) an Asiatic (Indian) pariah dog (*C. pallipes*); (c) the greyhound-type dog (*C. simensis*); and (d) a large mastiff-like dog, referred to as *C. molassus*. Humans encounter dogs as household pets, as work animals, and occasionally as wild or feral animals. Strains of dogs have long been bred for their special characteristics, and today there are more than a hundred established breeds of dogs. However, these are not inbred strains such as exist with mice (Ref. 46).

(2) *Clinical aspects.* Allergy to dogs, manifested by respiratory, conjunctival, and dermal symptoms, is quite common, usually easy to diagnose and simple to treat (Ref. 2). The true frequency of clinically significant allergy to dogs and of positive skin test reactions to dog epidermal extract in the general population with significant exposure to dogs have not been determined.

The frequency of positive skin tests in allergic populations is reported to be between 5 and 27 percent, as noted in Berrens' review (Ref. 1). Rynes (Ref. 3) observed 141 positive reactions to dog epidermal extract in 2,687 children and adults tested intradermally in an allergy clinic, a 5 percent rate of positive reactions. Among this entire group of allergic individuals, only 96 admitted having contact with dogs, and of this number, only 19 (20 percent) reported that they were aware of allergic symptoms produced by this contact.

Ohman (Ref. 58) reported that 38 (12.7 percent) of 300 consecutive patients seen in an allergy clinic because of asthma and/or rhinitis were aware of symptoms on exposure to dogs; nearly all of these symptomatic patients reacted by prick test to 1:10 (w/v) dog epithelial extract. The frequency of positive tests in patients who denied syptoms on contact with dogs was not reported.

Tuft et al. (Ref. 59) described the symptoms reported by 84 dog-sensitive patients. In this group, constriction in the chest followed by wheezing with or without cough was the commonest allergic complaint. Chest symptoms were frequently associated with or preceded by nasal symptoms (sneezing, watery rhinorrhea, and obstruction) and ocular symptoms (lacrimation and itching). Four patients reported chest, nasal, ocular, and skin (i.e., pruritus) symptoms; 17 reported chest, nasal, and ocular symptoms; 18 reported chest and nasal symptoms; 21 reported chest symptoms; 3 reported chest, ocular and/or skin but no nasal symptoms; 6 reported nasal and skin symptoms; 4 reported nasal and ocular symptoms; and 11 reported nasal, ocular, or skin symptoms alone.

The natural history of allergy to dogs has never been fully documented. According to Hannaway and Hyde (Ref. 4), the frequency of positive skin tests to dog epidermal extract increases steadily in allergic children from about 20 percent at age 1 year to about 50 percent at age 10. The accuracy of these figures is perhaps questionable because of the small number of subjects in each age range and the highly selected population that was studied. On the basis of Rackemann and Edwards' report (Ref. 12), one can be certain that clinically significant allergy to dogs sometimes remits spontaneously.

(3) *Product description.* Hide with hair intact, hair and dander, or hair alone (the presence of dander not being specified) are the source materials used in the production of dog epithelial extracts. The exact sources of these materials are not precisely specified in most of the manufacturers' submissions to FDA. Some did state that they are obtained from animal suppliers, veterinarians, or establishments that groom and clip dogs.

At least one manufacturer uses source material from different breeds (number of breeds not specified) "to keep the allergenicity of the final product as representative as possible." No manufacturer makes note of the state of health of the animals from which his source materials are obtained.

Details of the extraction process vary considerably; in every case, the raw material is defatted prior to extraction. The Panel found the following descriptions of the preparation of dog epidermal extracts. Vaughan and Black (Ref. 60) recommended that in preparing an extract of dog hair the animal should be clipped or shaved to get as much dander with the hair as possible. They suggested that clippings should be washed with carbon tetrachloride, air-dried, weighed, and then extracted in buffer (1 part clippings to 5 parts fluid, w/v) for 48 hours in the cold. Afterwards, the fat should be removed from the fluid phase with water-free ether, the pH adjusted to neutrality, and the extract sterilized by filtration.

Holford-Strevens (Ref. 48) prepared an extract by mincing a large piece of whole dog skin, defatting it in ether and then extracting it in Coca's solution for 7 days. The aqueous extract was then Seitz filtered, dialyzed, and lyophilized.

Berrens et al. (Ref. 37) obtained dander by clipping the hair close to a dog's skin with an electric razor. The hairs were weighed, washed twice with acetone, and filtered through No. 1 filter paper. The powdered defatted dander remaining on the filter was air-dried, weighed, and extracted for 1 day at room temperature, first in 1 percent NaCl/1 percent phenol, then 1 percent NaCl, and finally with water. Extracts were dialyzed against distilled water, then lyophilized.

Brands et al. (Ref. 31) prepared extracts from nondefatted material obtained by scraping the outer side of a dog's skin. A 10-percent (w/v) suspension of this material was extracted in 0.1M sodium bicarbonate solution with gentle agitation for 24 hours at 5 °C. The suspension was then filtered, and the resulting solution was centrifuged at 0 °C for 1 hour at 50,000 g. The supernatant containing the allergen was stored at −20 °C or lyophilized and stored at 5 °C.

Yman et al. (Ref. 23) evaluated dog epidermal extracts prepared in four different ways and found that they differed in relative potency by more than 300-fold. Assigning a value of 1 to the first preparation, the relative allergenic activity of the four preparations was as follows: (a) mixed hair and dandruff from a variety of breeds, defatted and then extracted with Evans solution (1/10, w/v), a relative potency of 1; (b) hair and skin scrapings from dachshund, defatted and then extracted with phosphate buffer (1/10, w/v) yields a relative potency of 0.2; (c) a commercial dog epidermal extract (10,000 PNU/mL), a relative potency of 0.05; and (d) mixed hair from the same batch as No. 1 extracted in the same way after removal of as much dandruff as possible (1/10, w/v), a relative potency of 0.003. In the same assay, undiluted dog serum had a relative potency of 2,000. The Panel found no other report in which different methods of manufacturing dog epithelial extract have been compared directly.

(4) *Composition.* Characterization of the allergens in dog epidermal extracts was initiated by Wodehouse (Ref. 48). Hooker (Ref. 28) suggested that different canine breeds probably have different dander allergens. Fagerberg and Wide (Ref. 29), on the basis of a study of skin test reactivity, bronchial provocation and RAST with two different mixed dog epidermal extracts and extracts from nine different individual dog breeds, also concluded that there are breed-specific allergens as well as allergens

common to the different breeds. They reported that it was uncommon (i.e., in only 4 percent) to find a positive skin test reaction with an extract from an individual breed in patients with a negative reaction to mixed breed extracts. Thirty-four percent of skin tests with individual breed extracts were negative in patients who had a positive reaction to mixed breed extract. However, in the absence of information about the potency of these extracts, the significance of these results is questionable.

Varga and Ceska (Ref. 30) analyzed commercial dog epidermal extracts prepared from two different dog breeds (viz., alsatian and boxer), using isoelectrofocussing in gel and direct RAST to estimate allergenic activity extracted from fel slices. They observed that the extract from alsatian skin was the more potent and heterogeneous, and they concluded that there may be qualitative differences in the allergenic determinants present in extracts prepared from different dog breeds. Alternatively, they suggested that these differences might only be quantitative.

More recently, Blands et al. (Ref. 31), employing more sensitive assay methods, found no evidence for breed-specific allergens in extracts of dog hair and dandruff from six different dog breeds, including three long- and three short-haired breeds. They did not both qualitative and quantitative differences between the individual breeds, but they attributed these differences to differences in the quality of the source materials, i.e., the antigen content in extracts from short-haired dogs was much greater than in extracts from long-haired ones, which they attributed to there being more dandruff relative to hair in the former. These variations in the relative concentrations of allergens present in extracts from different breeds of dogs may explain why dog-sensitive patients may react to only some dogs and not to others. Although this report indicates that there are no breed-specific allergens, it does require confirmation before the question is finally settled.

As mentioned above, Ohman et al. (Ref. 36) presented evidence for common allergens in cat and dog sera; their conclusion is based on RAST and RAST inhibition assays. Sera from horse, rabbit, rat, mouse, and guinea pig each showed much lower degrees of cross-reactivity; the significance of these latter cross-reactions was minimized by the investigators.

By crossed-line immunoelectrophoresis, Blands et al. (Ref. 31) found partial indentity between a number of antigens in dog epidermal extract and extracts of hair and dandruff from cat, cow, horse, guinea pig and sheep; sera from cat, horse and man; and, finally, extract of house dust. These investigators, in agreement with Ohman, found that the highest degree of cross-reactivity was between serum from dog and cat. An antigen cross-reacting with dog serum albumin was present in all the epithelial extracts except that from sheep, and in all three sera. Six antigens in house dust cross-reacted with antigens in dog epidermal extract.

Frankland (Ref. 61) pointed out that dog dander collected in the summer months may be contaminated by pollens.

Regarding the identity of allergenic proteins in dog epidermal extracts, Yman et al. (Ref. 23) reported that the most abundant allergenic protein in the extracts they studied was serum albumin. By polyacrylamide gel electrophoresis and direct RAST, other proteins including one in the gamma-globulin region were identified as minor allergens. These investigators regarded the serum proteins as responsible for the main part of the allergenic activity of dog dander.

Holford-Strevens (Ref. 48) fractionated dog skin extracts by sephadex gel filtration and found that the majority of the allergenic activity eluted in a position between 67,000 and 23,800 daltons; activity also was found in higher molecular weight material. Analysis of the pattern of skin test responses to these fractions in 15 test subjects suggested the presence of multiple allergens.

Varga and Ceska (Ref. 30) reported that the major allergenic activity of dog dander extract had a pI (pH at the isoelectric point) in the range of 4.3 to 4.7, i.e., close to that of serum albumin. Minor allergens in the broad pI range 3.0 to 8.5 reacted with antibodies in sera from certain dog-sensitive patients.

Glovsky et al. (Ref. 62) found that the majority of the allergenic activity in dog dander extract was in protein with molecular weights between 20,000 and 45,000 daltons; lesser amounts were found in fractions with molecular weights of approximately 10,000 daltons and others of up to 100,000 daltons. Immunoelectrophoretic analysis of the unfractionated extract using anti-whole dog serum showed bands consistent with albumin and gamma-globulin, another indication that serum components are present in dander extracts. Blands et al. (Ref. 31), using crossed immunoelectrophoresis, found 21 distinct proteins in epidermal extracts obtained from mixed dog breeds. All but five of these were serum proteins. Using CRIE, two major allergens and five minor allergens were detected in these extracts. Dog albumin was regarded as the most important of the two major allergens. Sera from 20 of the patients contained specific IgE antibody with high affinity for this protein. The second major allergen was not identified specifically. Three of the five minor allergens, i.e., those which reacted with only 25 to 50 percent of the 21 sera, were found to be serum proteins; one was identified as alpha-l-antitrypsin, the other as gamma-globulin. Four nonserum proteins among those in the epithelial extract were shown to be allergens, but they were not further identified. In contrast, McLean et al. (Ref. 63), who studied 10 dog-sensitive patients, found that skin test reactivity and RAST activity were greater with a partially purified extract of dander than with purified serum albumin in 9 out of 10 dog-sensitive patients.

In summary, there are a number of different allergens in dog epidermal extracts, and albumin is undoubtedly one of them. The relative amount of each varies in different extracts, especially in those from different breeds of dog.

(5) *Standardization.* There is no established standard of potency for dog epidermal extracts. The general comments made earlier for cat epidermal extracts apply as well to these extracts.

According to Varga and Ceska (Ref. 30), the potency of different commercial dog epidermal extracts may vary almost 1,000-fold. Furthermore, as determined by RAST, these authors found no correlation between the total protein concentration and the allergen content of extracts from four different commercial sources. By polyacrylamide gel isoelectrofocussing and RAST, three batches of dog epidermal extracts from a single firm showed a similar distribution of allergenic components. In contrast, an extract obtained from a different firm showed an altogether different pattern on the isoelectrofocussing gel. The pattern obtained with one extract after 10 months of storage at 4° C was significantly different from its original "components spectrum," pointing to an instability of some of the allergenic components in this extract.

The Panel found no other report on the potency or the stability of dog epidermal extract.

(6) *Labeling.* Currently available products are labeled "Dog", "Dog Dander", "Dog Epithelia", "Dog Hair", "Dog Hair and Dander-Mixed Breeds",

"Chihuahua", "Poodle, French" and "Poodle, Hair". Frankland (Ref. 61) stated: "An allergenic extract labeled 'Dog' or 'Mixed Dogs' does not give us enough information about the extract". Refer to the general statement on labeling for further comments.

(7) *Safety.* No information was provided by the manufacturers, and the Panel found no report in which either short-term or long-term safety of dog epidermal extracts for use in diagnosis and therapy had been studied. Tuft et al. (Ref. 59) noted a single constitutional reaction of increased wheezing some hours after a therapeutic injection in 3 of 84 dog-sensitive patients being treated with alum-precipitated pyridine extract of dog epidermis. Six patients in this series had a local reaction on one occasion, and eight patients had local reactions on several occasions during the course of this therapy.

McLean et al. (Ref. 63) recently pointed out that dog epidermal extracts contain potent antigens such as serum albumin and, therefore, particularly after high dosage, may induce circulating immune complexes. Although this is a theoretical consideration, they suggested a cautious approach to immunotherapy.

Refer to the general statement on safety for other comments.

(8) *Effectiveness*—(i) *For diagnosis.* Virtually no data were provided by the manufacturers on the effectiveness of their extracts for the diagnosis of allergy to dogs. Nevertheless, it is well documented that immediate skin test reactions to various dog epithelial extracts are induced in clinically sensitive individuals. Some of this evidence is cited above; summaries of other reports follow.

Rynes (Ref. 3) did intradermal skin tests in adult patients with an extract called "dog dander" containing 10 mg of protein nitrogen per mL; children were tested with a 10-fold lower dose. As noted above, 5 percent of 2,750 tests in 2,687 allergic patients were positive. Of the individuals with a positive test, only 20 percent had recognizable symptoms when they had contact with a dog.

Fontana et al. (Ref. 54), using a commercial dog dander extract containing 1,000 PNU per mL, intradermally skin tested 194 allergic (although not necessarily allergic to dogs) children and 100 normal children between the ages of 2 and 11 years attending a general pediatric outpatient clinic. None of the normal children had a positive reaction while 24 percent of the allergic children did. This was virtually the same result they obtained with cat dander extract in the same children.

Sarsfield et al. (Ref. 52) tested 36 allergic children who had contact with dogs without admitted clinical sensitivity to dogs and found that 23 (63 percent) had a positive prick test reaction to the commercial extract, but only three (8 percent) of these children had a positive RAST for dog allergen. Of 13 children who admitted having symptoms on exposure to dogs, all had a positive skin test reaction to dog epidermal extract and seven (54 percent) had a positive RAST. Thus, these authors concluded that a clinical history of symptoms on exposure to the source of the offending allergen is a more accurate indicator of allergy than is the skin test. The skin test is probably too sensitive a test; the assay for serum antibody being less sensitive may therefore be a more accurate index of clinically significant allergy. Fagerberg and Wide (Ref. 29) found that RAST was positive in 26 adult asthmatic patients who were clinically sensitive to dogs whereas RAST was negative in 7 other asthmatic patients who were not clinically sensitive to dogs. In this report, either the positive or negative results of skin tests and RAST agreed in 85 percent of their cases. Özkaragöz et al. (Ref. 64) also compared the results of skin tests and RAST in 30 allergic patients; there was agreement between the tests in 83 percent of the cases. They reported no comparison of these test results with clinical histories.

Thus, the status of the effectiveness of dog epithelial extracts is the same as it is for cat epithelial extracts, namely, that unstandardized products generally induce positive reactions in individuals who are clinically sensitive to dogs and no reaction in most nonallergic individuals but they do induce positive reactions in a significant proportion of allergic individuals who deny that they are allergic to dogs.

(ii) *Effectiveness for therapy.* No data were provided by the manufacturers to demonstrate the effectiveness of their extracts in the treatment of allergy to dogs. The Panel found no reports of controlled clinical investigation of the effectiveness of this extract, one report of an uncontrolled study which describes the results of treatment with an aqueous dog epithelial extract and several uncontrolled, mainly anecdotal reports of therapy with a pyridine extracted, alum precipitated (Allpyral™) extract. Summaries of these reports follow.

Brown and Wolfe (Ref. 56) treated 12 dog-sensitive patients with aqueous dog epithelial extract for a minimum of 9 months, a maximum of 5 years, the dosage ranged from 150 to 5,000 PNU per injection with a mean of 1,850. The results of treatment were evaluated subjectively. Two of these patients reported definite improvement, having no allergic symptoms when in contact with a dog for 24 hours; two had partial improvement with fewer symptoms on contact for 24 hours; and 8 reported no improvement.

Brown and Wolfe (Ref. 56) treated 38 other patients with Allpyral™ dog epithelial extract. In these patients the doses ranged from 800 to 14,000 PNU per injecion. Five patients reported definite improvement, six partial improvement and 27 no improvement. Brown and Wolfe concluded that both types of extract were ineffective in most patients.

Two brief reports of uncontrolled studies suggested that Allpyral™ extract of dog epithelium provided significant clinical improvement in dog-sensitive patients. Gould (Ref. 65), in an abstract, stated that 11 patients previously treated unsuccessfully with aqueous extracts developed significant tolerance to dogs following therapy with the Allpyral™ extract. Scherr (Ref. 66) stated in a short letter that 25 of 27 dog-sensitive patients were improved after therapy with Allpyral™ extracts.

Tuft and Torsney (Ref. 55) studied 17 dog-sensitive patients and reported the results of treatment with an Allpyral ™ extract of dog dander. No control group was included in this study. All of these patients had definite allergic symptoms when exposed to dogs or had perennial symptoms plus frequent or constant exposure to the animal. All had positive skin test reactions (as well as positive conjunctival reactions) to aqueous dog epithelial extract. All of these patients either would not or could not avoid contact with dogs so they were a highly selected group. Most of the patients were also allergic to other inhalant allergens and were being treated for these allergies by environmental control or immunotherapy or both. None of the patients had previously been treated with aqueous dog epitherial extract. Injections were given at weekly or 2-week intervals until an optimum dose was reached. This dose varied from 2,000 to 5,000 PNU with an average of 3,900 PNU. When the optimum dose was reached, injections were given thereafter every 4 weeks or longer. Local reactions followed 4.5 percent of the injections. Thirteen of the 17 patients (76 percent) reported fewer symptoms on exposure to dogs after 3 to 10 months of therapy. Two patients reported no change and two others had no further exposure to dogs during the period of observation. The authors concluded that immunotherapy with Allpyral™ extract

of dog dander is "worthwhile" for those dog-sensitive individuals who cannot avoid contact with these animals.

In a more recent paper, Tuft et al. (Ref. 59) reported the results of their further study of the effectiveness of immunotherapy with Allpyral™ extracts in animal-sensitive patients. Eighty-four dog-sensitive subjects (26 up to 16 years, 58 were 16 years and over) were included in this study. All had histories of symptoms following contact with dogs. Forty-three of 47 patients who were skin tested with dog epidermal extract ("routine testing strengths") had positive reactions. Treatment was prescribed because the patients could not or would not avoid exposure to dogs. Again, no control group was included in this study. In the majority of patients, the maximum tolerated dose was reached by the 25th injection; it ranged between 600 and 5,000 PNU and was usually given at 3- to 5-week intervals. Treatment was given for up to 1 year in 26 patients, for 2 to 3 years in 32 and for 4 or more years in 26. It was discontinued if the patient was unlikely to have further contact with dogs. With more than 3,000 injections given, the incidence of local reactions was 2.5 percent and of constitutional reactions about 0.2 percent. Clinical improvement was estimated solely on the basis of the patients' subjective reports. Sixty-two patients (74 percent) reported fewer symptoms on exposure to dogs, 16 (19 percent) reported no change, and the result was not determined in 6 (7 percent) others. The authors again concluded that immunotherapy with Allpyral ™ extract of dog dander was an effective form of therapy and that it was safe.

(9) *Critique and conclusions.* The manufacturers provided no reliable data on the effectiveness and safety of dog epidermal extracts for use in diagnosis and therapy.

Hair obtained by clipping dogs is commonly used as the raw material in the manufacture of these extracts. On the basis of one study, this would appear to be an adequate source material so long as the dander is included with the hair. Dog pelt has not been adequately evaluated as a raw material, but comments made about cat pelt would presumably apply.

The need for breed-specific extracts is uncertain. The most recent data suggest that there are no breed-specific allergens. Rather, there are quantitative differences between extracts prepared from the hair and dander of different breeds of dogs. Therefore, extracts should be prepared from source material obtained from a sufficiently large variety of breeds and/or mongrel dogs to assure an adequate sample of all the dog allergens. Unless evidence is obtained to the contrary, the Panel sees no need to retain breed-specific allergens on the market.

The identity of the principal allergens in dog epidermal extracts has not yet been established, although serum albumin appears to be one of them. Cross reactivity of antigens in dog epidermal extract and in dog serum compared with antigens in epidermal extracts and serums of other animal species has been described, but its significance in allergic disease has not been determined.

There is currently no reference standard or standard of potency for dog epidermal extracts. Commercial extracts vary significantly in potency. To what extent this may be due to differences in manufacturing (including the source material, its preparation, storage and extraction, etc.) has not been determined. Nevertheless, it should be possible to establish a reference preparation and apply available methods to ensure adequate potency of dog epidermal extracts.

Allergy to dogs occurs with about the same frequency as allergy to cats, i.e., it is one of the most frequently encountered allergic sensitivities. Comments made above about the relatively high frequency of positive skin tests to cat epidermal extract in individuals who are allergic but who are not allergic to cats apply equally well to dog epidermal extract. This probably means that the skin test with dog epidermal extract, as generally employed, is too sensitive to permit the differentiation of clinically significant allergy to dogs in allergic individuals. The availability of standardized extracts which could be used in a more quantitative type of skin test might resolve this issue.

Regarding the use of this extract in therapy, there are no reports of controlled clinical trials in dog-sensitive patients. The results of one uncontrolled trial with an unstandardized aqueous dog epidermal extract suggest that this therapy is not effective in most patients who suffer from allergic sensitivity to dogs. This report contains no data on the immunologic parameters of this disease. Reports of the use of Allpyral™ dog epidermal extracts are equally deficient. In general, those writing on the subject usually reserve therapy only for individuals who cannot avoid contact with dogs.

In conclusion, the Panel believes that there is sufficient evidence to state that dog epidermal extract, properly manufactured and standardized against an accepted reference preparation, is effective for the diagnosis of allergy to dogs. The therapeutic effectiveness of dog epidermal extract has not been established and requires an objective, well-controlled clinical trial with appropriate immunologic studies.

(10) *Recommendations.* It is recommended that dog epidermal extract be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

c. *Horse (Equus caballus)*—(1) *General description.* The horse is a mammal of the family *Equidae.* It comprises a single species, *E. caballus,* whose numerous varieties (including the pony) are called breeds. Other species of the family *Equidae* include the asses (such as the donkey) and the zebra. The mule is the hybrid offspring of a male ass and a femal horse (Ref. 46).

(2) *Clinical aspects.* Allergy to horses, manifested principally by respiratory and dermatologic symptoms, was at one time one of the commonest allergies (Ref. 60). Early reports of allergy to horses include those of Goodale (Ref. 67), de Besche (Ref. 68), Walker (Ref. 69), and Rackemann (Ref. 70). However, with the disappearance of horses as a common mode of transport and as work animals, the incidence of allergic sensitivity to horses has decreased. Such sensitivity still is found among amateur and professional riders, stable attendants, farmers, and veterinarians. Workers who handle horse hides for commerical purposes may become sensitized and exhibit typical respiratory symptoms as well as urticaria. Horse hair is used in the manufacture of a number of household items, including mattresses, furniture and rug pads, and in the manufactuer of felt; but the allergenic potential of horse hair itself (which is cleansed of dander prior to use) is probably not significant. It was well known that many individuals sensitive to horse serum (usually as a consequence of the administration of a specific antiserum) were also sensitive to horse dandruff, although the reverse was apparently less common (Ref. 71).

The frequency of clinically significant allergy to horses and of positive skin test reactions to horse epidermal extract in the general population or in a population exposed to horses has not been determined. Fontana et al. (Ref. 54) reported that 2 out of 100 apparently nonallergenic children between the ages of 2 and 11 years had a positive skin test to horse dander extract. In seven different reports summarized by Berrens (Ref. 1), the incidence of positive skin test reactions in allergic subjects ranged from 8 to 44 percent. In the largest of the

groups studied, Rynes (Ref. 3) observed positive reactions in 211 of 2,750 patients tested, an 8 percent rate of positive reactions. Fontana et al. (Ref. 54) reported a 19 percent incidence of positive skin reactions to horse dander extract among 168 allergic children.

The natural history of allergy to horses is not documented but it must be at least as variable as allergy to other animals. Avoidance of contact with horses and their emanations clearly eliminates symptoms associated with exposure to them (e.g. Ref. 12).

(3) *Product description.* Horse hair and/or horse dander are the source materials used by the manufacturers in the production of horse epidermal extract. In most cases, the exact source of these materials is not specified in the manufacturers' submissions to the FDA.

One manufacturer collects horse hair in February, March or April, when the winter coat begins to shed and the hair is most easily removed. Dander may be obtained at other times during the year but the amount is usually greatest in the winter coat. The animal is first curried to remove debris. Then, long hairs are removed with clippers. Hair over the withers, back, and rump is collected by running the clippers close to the skin. The clippers are followed by a portable vacuum. Samples containing less than 1 percent foreign material (as determined by microscopic examination) are pooled for subsequent processing.

Details of the extraction process vary considerably from one manufacturer to another. No study of the variables in this process (e.g., temperature, duration, pH, etc.) has been made. Forster (Ref. 72) extracted 5 gm of dry dander in 100 mL of 0.85 percent NaC1 by shaking with glass beads. Masses of small hairs present in these suspensions were removed by centrifugation. The pH of these suspensions was 7.2 to 7.6. They were shaken for 4 to 5 hours, centrifuged, and the supernatants were sterilized by filtration. Squire (Ref. 21) started with dandruff obtained by brushing and combing horses at a serological institute. The hair was eliminated by shaking the material with ether and then pouring the suspension through a Buchner funnel. The epidermal scales in the effluent were then captured on filter paper, rinsed with fresh ether, to remove additional fat, and then dried. For extraction, this powdery residue was rubbed up with toluene, then with 0.9 percent NaC1 solution to give a cream. Additional saline was added to give a final proportion in the extraction of 1 gm dander, 1 mL toluene, and 15 mL saline. Extraction was carried out at room temperature (12° to 20° C) for 3 days, and the suspension was then filtered. The resulting extract was a clear solution, light brown in color.

Stanworth (Ref. 22) obtained crude horse brushings and freed this material from hair by suspensing it in cold acetone and then pouring it through a Buchner funnel. After evaporating the acetone, the resultant dried, defatted powder was extracted for 3 days with 0.85 percent saline-containing toluene as a preservative. Insoluble epidermal material was removed, leaving crude dandruff extract. After dialysis, the extract usually contained about 1 percent protein.

Silver and Bookman (Ref. 73) obtained dander by vacuuming groups of animals pooling the powdery epidermal material thus obtained and mixing it in Coca's solution. This suspension was then frozen and thawed several times to fragment any intact cells. After filtration, the solution was precipitated in the cold in 70 percent acetone. The resulting precipitate was vacuum dried and subsequently dissolved in buffer for use in skin testing. Ponterius et al. (Ref. 24) extracted defatted horse brushings with Evans' solution. All of the above procedures resulted in potent extracts.

(4) *Composition.* Characterization of the allergens in horse epidermal extracts was initiated by Wodehouse (Ref. 49). He recognized that horse epidermal extract contained at least two allergenic protein components, one of which was regarded as epidermal in origin, the other being derived from serum. Tuft (Ref. 74) recognized that some atopic patients were sensitive to the dander allergen, others to the serum allergen and some to both allergens. Squire (Ref. 21) demonstrated the presence of common antigens in horse serum and dander extract by quantitative precipitation. He regarded albumin as being the most likely candidate for the major common antigen. Stanworth (Ref. 22) used gel precipitation, with rabbit antiserum raised against crude dander extract, to examine the composition of dander extracts. The major allergenic activity determined by skin test in horse-sensitive subjects was found in a protein fraction with Beta-2 electrophoretic mobility. The cross reaction between dander extract and serum was found to be due to the presence of serum albumin and globulin in danger extracts. Ceska and Hulten (Ref. 51) analyzed fractions of dander extract, separated by isoelectrofocussing in polyacrylamide gel by direct RAST. Several peaks of activity were found, the principal allergenic activity being at pI 4.2. Ponterius et al. (Ref. 24) studied several horse epidermal extracts and horse serum, with RAST, polyacrylamide gel electrophoresis, and immunoelectrophoresis. Serum albumin was found to be an important allergen in the epidermal extract. Its concentration varied considerably in the different preparations. For example, the concentration of serum albumin in a commercial preparation was more than a million times greater than it was in an extract prepared from horse dander brushings by these investigators. In addition to albumin, two other allergenic proteins were found in the dander extract. Their molecular weights were 38,000 and 22,000 daltons; the pI of the latter was 4.2. Sera from 50 allergic patients were studied by RAST, using a crude dander extract, an allergenic fraction from the dander extract and horse serum as the test allergens. Twenty-four percent of the patients had IgE antibody specific for serum proteins; 62 percent had IgE antibody specific for dander proteins, and 14 percent had antibodies specific for both types of allergens.

An extensive analysis of the allergens of horse dander and hair has recently been reported in a series of papers by Lowenstein and his colleagues (Ref. 26). Their starting material was dander and hair obtained by vacuuming horses; it was extracted 1:10 w/v in 0.125 M ammonium bicarbonate, pH 7.6, with 0.015 M sodium azide, overnight at 5 °C. The mixture was the filtered and centrifuged in the cold, dialyzed, freeze-dried, and stored at 5 °C. For subsequent analyses, a solution of this material containing 14.25 mg/mL was used. A commercially prepared freeze-dried extract of hair and dander was also used (as a 5-percent w/v solution) in these studies. In addition, the authors prepared a solution of hair proteins from hair that had been thoroughly washed in cold running distilled water; proteins were solubilized by reduction and alkylation. QIE using rabbit antibodies revealed that the danger extract contained 25 antigens, of which several were mutally partially identical; four were serum-specific; and none showed partial identity to solubilized hair proteins. Partial identity to antigens of sera and dander extract of cow, dog, cat and guinea pig, and house dust extract was observed. Cross reactivity with antigens from other *Equidae* was not studied. By means of CRIE, three proteins, antigens No. 6, 9 and 11, were identified as being the major allergens in the danger extact. Antigens No. 13 and 16 to 18 were identified as minor allergens, i.e., sera from less than one third of the patients contained IgE antibodies which bound these antigens. The authors regarded their antigens No.

6 and 11 as equivalent to the 22,000 and 38,000 dalton allergens of Ponterius et al. (Ref. 24). The three major allergens were isolated to better than 95 percent purity. Their molecular weights were 19,000, 51,000 and 31,000 daltons; their pI's were 4.1, 3.8, and 3.9, respectively. Amino acid analysis of the isolated allergens revealed large variations in their amino acid composition which could be responsible for their different reactivities in RAST inhibition and different apparent concentrations as measured by the Lowry assay.

(5) *Standardization.* Currently there is no standard of potency for horse epidermal extracts.

Ceska et al. (Ref. 51) reported wide variations in the allergenic activities (as determined by direct RAST) of horse dander extracts prepared by five different manufacturers. The total nitrogen content of these extracts did not correlate with their allergenic activity.

Longcope et al. (Ref. 44) reported that horse dander extract was not detectably inactivated when heated at 100 °C for 1 hour at pH 7.4 or 9.0, whereas it lost much of its activity when heated at pH 4.5.

Markussen et al. (Ref. 11) demonstrated that allergenicity of horse dander extract was unaffected by dialysis, ultrafiltration, and freeze-drying. The predominant antigens in this extract were not altered during storage in the cold for up to 44 hours at pH values ranging from 4.0 to 8.0. Proteolytic enzymes, pepsin in particular, degraded the major antigenic components to a significant degree.

Koers et al. (Ref. 75) reported that ammonium sulphate-precipitated, lyophilized horse dander protein prepared in 1962 (from material provided by Stanworth) retained its full allergenic potency for 15 years.

The Panel found no other reports on the potency or the stability of horse epidermal extract.

Refer to the general statement on standardization for further comments.

(6) *Labeling.* Currently available products are labeled "Horse Hair" or "Horse Dander." Refer to the general statement on Labeling for further comments.

(7) *Safety.* The Panel found no report in which either short-term or long-term safety of these extracts for use in diagnosis and therapy had been studied. Ratner and Gruehl (Ref. 20) stated that horse dander extract, presumably undiluted, may have a primary toxic effect in guinea pigs if more than 2 mL are injected intravenously. However, it is unlikely that an equivalent dose would be administered to humans. Some patients who are allergic to horse dander are sensitive to horse serum proteins, and the therapeutic administration of horse antitoxins to such individuals may induce systemic allergic reactions (Ref. 76).

Refer to the general statement on safety for further comments.

(8) *Effectiveness*—(i) *For diagnosis.* No data were provided by the manufacturers on the effectiveness of their extracts for the diagnosis of allergy to horses. At the same time, the medical literature contains abundant evidence showing that immediate skin test reactions are induced by horse epidermal (mainly dander) extracts in clinically sensitive individuals (Refs. 74 and 77). That this reactivity is due to specific IgE antibodies has been demonstrated both by passive skin transfer (Ref. 74) and by RAST (Refs. 24 and 51).

Allergy to animal allergens is usually evident from the clinical history, especially with respect to horse dander according to Rynes (Ref. 3). The reliability of the skin test in providing an accurate diagnosis of clinically significant allergy to horses is still open to question. This could be related in part to variability in allergenic composition and potency of extracts used in various studies, in which extracts of unknown composition and undetermined potency were employed. The situation is complicated further by the fact that different individuals vary considerably in their sensitivity to different components in the same extract. (Ref. 78).

Leegaard and Roth (Ref. 79) reported an overall agreement in 79 of 87 patients (91 percent) ranging in age from 3 to 23 years between a prick test response of at least 3 plus to horse dander extract, at a maximum concentration of 1:100 w/v, and the clinical history judged as being improbable, probable, or indefinite.

On the other hand, several investigators have found positive skin tests with horse epidermal extracts in a significant proportion of allergic individuals with no clinical symptoms related to contact with horses. In Rynes series of 40 allergic patients with a positive skin test to horse dander extract, 15 reported no symptoms on contact with horses (Ref. 3). In a more recent study, it was reported that only 11 percent of 61 asthmatic patients with a positive skin test had a clinical history of allergy to horses (Ref. 80). Koers et al. (Ref. 75) found, in a group of atopic individuals, that only four of five persons with a clinical history of allergy to horses had a positive skin test to horse epidermal extract; and 14 of 18 persons with a negative history had a positive skin test reaction. They concluded that skin test results in atopic patients were often unrelated to clinical evidence of allergy to horses.

Several studies suggest the accuracy of diagnosis of clinically significantly allergy to horses is improved by the addition of RAST and/or bronchial provocation testing (Refs. 81 through 83).

(ii) *Effectiveness for immunotherapy.* The Panel found no reports of clinical trials with horse epidermal extract in the treatment of allergy to horses. Most allergists recommend avoidance of the animals as the preferred means of therapy.

Several uncontrolled case reports representing a total of nine patients describe treatment with Allpyral™ extract of horse dander of undetemined potency. None of these reports includes an objective assessment of clinical exposure or of clinical response, nor do they include any immunologic studies. Scherr (Ref. 66) reported that three horse-sensitive patients had increased tolerance to horses after treatment with an Allpyral™ extract of horse dander. Tuft and Torsney (Ref. 55) reported that four horse-sensitive patients had improved tolerance after 3 to 10 months of therapy with Allpyral™ extract of horse dander. Maintenance doses ranged from 2,000 to 10,000 PNU. Local but no constitutional reactions to the injections were observed. Brown and Wolfe (Ref. 56) treated two horse-sensitive patients, ages 8 and 15 years, with Allpyral™ extract of horse dander. Monthly maintenance doses were 6,000 to 10,000 PNU, respectively. The patients also received concomitant therapy with various other allergens. It was reported that the 8-year-old individual who previously experienced angioedema and urticaria and the 15-year-old who had experienced nasal and conjunctival symptoms both developed increased tolerance to horses.

(9) *Critique and conclusions.* Allergy to horses, by which is meant allergy to the epidermal emanations from horses but not reactions to injected serum, may be less frequent today than it was 50 years ago.

The source material used in the manufacture of horse epidermal extracts usually consists of both dander and hair as well as a variable amount of other substances, some of which are not from the horse. The hair itself if probably not allergenic. Neither the manner in which it is obtained nor the source material itself is standardized. There is no requirement that the animals from which the source material is obtained should be healthy.

Methods of extraction of the source materials vary widely, resulting in extracts which vary widely in composition and potency. There is no established standard of potency for these extracts. Because there appear to be three major allergens in an extract of horse dander, the extracts at least should be standardized in terms of the content of all three of these allergens. The stability of aqueous dander extracts is unknown. The labeling is not always correct in that some extracts are labeled "Horse Hair," others "Horse Dander," when in fact the source material may contain both hair and dander and the extract contains little if any protein from the hair itself.

Extracts of horse dander can induce immediate skin test responses in most individuals who are allergic to horses and induce immediate skin test reponses in some individuals who are sensitive to horse serum. These extracts will also elicit skin reactions in individuals who have no clinical history of allergy to horses, particularly if they are sensitive to other allergens. The significance of these apparently falsle-positive responses is still uncertain and needs additional investigation.

There are no adequate clinical studies on the effectiveness of horse dander extracts for use in therapy. The few available case reports on the use of Allpyral™ extracts of horse dander provide inadequate evidence for the effectiveness of this material. There is virtually no data on the short-term and long-term safety of horse dander extracts as used in therapy.

In conclusion, the Panel believes that there is sufficient evidence to state that horse epidermal extract, properly manufactured and standardized against an accepted reference preparation, is effective in the diagnosis of allergy to horses. The therapeutic effectiveness of horse epidermal extract has not been established and requires an objective, well-controlled clinical trial with appropriate immunologic studies.

(10) *Recommendations.* It is recommended that horse epidermal extract be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

5. *Extracts derived from other common domestic animals*—a. *Cattle (Bos taurus)*—(1) *General description.* Cattle are large bovine animals belonging to the ox tribe, along with the bison, yak, and water buffalo. Female cattle are called cows; males are called bulls; and the young are called calves. Cattle are a common source of meat, milk, hides, and other products (Ref. 46)

(2) *Clinical aspects of allergy to cattle.* Cattle are a cause of respiratory allergy in farmers, herdsmen, and veterinarians, but the frequency of this allergy to cattle is unknown. In urban areas, exposure to this animal is rare, except in slaughter houses. At one time padding under rugs and carpets was made from felted cattle hair and was a common source of exposure. In 1954 (Ref. 2), this was said to be the most important source of allergy to cattle dander. Cattle hair is used in typewriter pads, mattress and toy stuffing, and cheap felted goods; and these materials were also regarded as a source of cattle dander allergen (Ref. 60).

The natural history of allergy to cattle has not been documented. Osvath et al. (Ref. 84) stated that "children giving a positive skin reaction to cow's hair have suffered from eczema in infancy with significantly higher frequency than asthmatic patients with a negative reaction." This conclusion was reached after study of 176 asthmatic patients. They concluded further that allergy to milk in infancy may lead to respiratory allergy to cow's hair in childhood. In their study, among 9 children with allergy to cow's milk manifested as asthma after consumption of milk, 7 had a positive response when skin was tested with milk protein, and all 9 had a positive skin test response to 100 PNU of a cattle hair extract. Six of these children also had a positive bronchial provocation test with the extract; three of them lived in the vicinity of a cow shed. Five other children who were not allergic to cow's milk had a positive skin test response to cattle hair extract. Two of these children, both of whom lived in the vicinity of a cow shed, also had a positive bronchial provocation test with cattle hair extract. The authors stated that sensitization to cattle epidermal allergens may occur as a result of ingestion of milk; however, other sources were not ruled out. Although nonreaginic antibodies to bovine serum albumin (BSA) were reported to be present in the serum of approximately three-fourths of normal infants (Ref. 85), it is likely that this immune response is seldom associated with respiratory allergy to cattle dander.

The frequency of clinically significant allergy to cattle and of positive skin test reactions to cattle epidermal extract have not been determined accurately in the general population or in populations at risk. Feinberg (Ref. 2) stated that, among patients in his private allergy practice, 7 percent had a positive skin test to cattle hair extract. Among a group of allergic agriculturists, 73 percent were reported to be allergic to cattle by skin test (Ref. 86).

Data submitted to the Panel by one manufacturer show that one nonallergic subject in thirty-four reacted to a 1:1,000 w/v solution of cattle hair extract, while 11 of 95 allergic patients reacted to the same solution (Ref. 126).

(3) *Product description.* Most manufacturers use cattle hair with dander as the source material for the production of cattle epithelial extract; one uses hide. The exact source of these materials is not specified in most of the manufacturers' submissions to FDA. One manufacturer stated that hides from healthy animals are obtained from local collectors; the method of certifying the health of the animals is not specified. A State university is the origin of the hair and dander used by one. Others obtain hides from "reputable collectors or processors." Several manufacturers state that they purchase source material as needed and do not store it for a prolonged period.

One manufacturer cuts the hairs into smaller pieces and mills them prior to extraction. Several specify that hairs are defatted with anhydrous diethyl ether prior to extraction. Details of the extraction process vary considerably from one manufacturer to another; most give no details for this particular extract. Some extract with Coca's solution, 1:10 w/v. In one case, extraction is done with glycerinated Coca's solution for 72 hours at room temperature with intermittent stirring. In this case, solids are removed by filtration through paper and Seitz filter pads. Sterilization is accomplished by filtration through a 0.22-micron membrane under positive pressure.

Eriksson et al. (Ref. 83) removed the hair from curry-combings of cattle by gentle washing in cold acetone. Defatted, dried dander was obtained after evaporating the acetone. An extract was prepared in saline-containing extraction fluid (with 0.5 percent phenol); extraction time was 2 to 4 days.

(4) *Composition.* Osvath et al. (refs. 84 and 87) demonstrated that cattle hair extract contains bovine serum albumin and alphaglobulin. In addition, it contains two protein fractions with molecular weights of approximately 20,000 daltons; these are not serum proteins.

Ceska and Hulten (Ref. 51) characterized commercial cattle dandruff extracts by isoelectricfocussing in polyacrylamide gels followed by direct RAST with material extracted from gel slices. The "major allergenic components," i.e., the more active allergenic regions of the gels, were in the pI range of 3.80 to 5.00. They also found that the spectrum of the reactive

components depended on the serum used for testing.

In a study of horse epithelial extract, Markussen et al. (Ref. 11) reported finding several antigens which were identical or partially identical to antigens in cattle hair extract and serum, using crossed-line immunoelectrophoresis.

(5) *Standardization.* Currently there is no standard of potency for cattle epidermal extracts.

Ceska and Hulten (Ref. 51) assessed the allergen content of cow dandruff extracts by a direct RAST method and found large differences in the activity of several commercially prepared extracts. Furthermore, they found no correlation between dose response curves in the RAST and the total nitrogen content of these extracts.

The Panel found no other reports on the potency or the stability of cattle epidermal extract.

Refer to the general statement on standardization for further comments.

(6) *Labeling.* Currently available products are labeled "Cattle Hair," "Cattle Hair and Dander," "Cow," "Cow Dander" and "Cow Epithelium."

Refer to the general statement on labeling for further comments.

(7) *Safety.* The Panel found no report in which either the short-term or long-term safety of these extracts for use in diagnosis and therapy had been studied.

Refer to the general statement on safety for further comments.

(8) *Effectiveness*—(i) *For diagnosis.* No data were provided by the manufacturers on the effectiveness of their extracts for the diagnosis of allergy to cattle. Nevertheless, immediate skin test responses have been elicited by cattle epidermal extracts in individuals with a clinical history of allergy to cattle (Refs. 2 and 84). That this reactivity is due to IgE antibodies has been demonstrated by RAST (Ref. 57).

The Panel found no systematic study of the effectiveness of this extract for diagnosis of allergy to cattle. Berrens et al. (Ref. 40) observed a negative prick test with cow dander extract (0.5 mg of nondialyzable material per mL) in an allergic patient who had had symptoms upon contact with cattle; this patient did have positive reactions to horse dander extract, cat hair extract and guinea pig hair extract. He attributed the negative reaction to cattle dander extract to the very low allergen content of the extract. Ten other allergic subjects who had no clinical history of allergy to cattle had negative prick tests with the same dander extract.

Eriksson (Ref. 88) found a very strong positive correlation between intradermal skin test results and bronchial and/or nasal provocation tests with cattle dander extract in 70 patients referred to an allergy clinic because of asthma and/or allergic rhinitis from various causes; few of these patients were actually allergic to cattle. However, the agreement between the skin tests and negative provocation tests with this extract was only 40 percent, lowest among the four animal epithelial extracts used. Apparently, the greater the skin sensitivity (i.e., elicitation of a reaction with more highly diluted extract), the greater was the likelihood of a positive reaction being clinically significant. Eriksson et al. (Ref. 83) also report significant positive correlations between RAST and skin tests results in 121 cases and between RAST and test results in 63 cases, using cattle dander extract.

(ii) *Effectiveness for immunotherapy.* The Panel found no reports of clinical studies with cattle epidermal extract in the treatment of allergy to cattle. However, it has been used occasionally to treat occupationally related allergy to cattle, but the results of such treatment have not been reported.

(9) *Critique and conclusions.* There is no doubt that cattle are a source of allergen which can sensitize individuals who are sufficiently exposed to these animals. The frequency of allergy to cattle (excluding allergy to bovine proteins encountered as food) is unknown. It is presumably most frequent among those who maintain or are employed around cattle. It has been postulated that some infants who develop allergy to proteins in cow's milk may experience respiratory allergic symptoms on later exposure to cattle, but this is not certain.

Cattle epidermal extracts are usually prepared from hair which also contains dander; this may explain the reportedly low allergen content of some of these extracts.

There are insufficient data on the character and specificity of cattle-derived allergens. There is no established standard of potency for cattle epidermal extracts. The effectiveness and safety of these extracts for diagnosis and therapy of allergy to cattle has not been demonstrated.

(10) *Recommendations.* The Panel recommended that cattle epidermal extract be placed in Category IIIA for both skin test diagnosis and immunotherapy. One Panel member recommended Category I for diagnosis, believing cattle epithelial extract to be as good as horse epithelial extract.

b. *Goat (Capra)*—(1) *General description.* Goats belong to the cattle *(Bovidae)* family. True goats make up the genus *Capra;* the Rocky Mountain goat is classified as the genus *Oreamnos.* There are many species of wild and domestic goats. The latter are a source of milk, flesh, hair, and hide. Goats are normally covered with straight hair, but some species grow wool underneath. *Angora* and *Cashmere* are breeds raised for their valuable hair. (Most commercial "cashmere" fabrics are made with sheep wool.) Angora hair is used in the manufacture of mohair. The alpaca, a species of llama, is a domestic goat of Peru whose fleece is used in yarns (Ref. 46).

(2) *Clinical aspects.* Clinical evidence of allergy to goats is uncommon even in individuals who have close contact with them (Refs. 2 and 62). According to Feinberg (Ref. 2), respiratory allergy to goat hair may occur where goat hair is used in bedding. Contact dermatitis to goat hair has been reported (Refs. 89 and 90). However, according to Vaughan and Black (Ref. 60), goat hair which has been processed for use in manufacture is an unlikely source of allergen. Therefore, where processed goat hair is the alleged allergen, a contaminating allergen or a nonimmunologic mechanism may be operative.

(3) *Product description.* These products are available as goat epithelial, dander and hair extracts. Both aqueous and glycerinated extracts are marketed, either as weight per volume (1:5 through 1:10,000) or protein nitrogen unit (10 through 20,000 PNU per mL) solutions.

The source materials for the manufacture of goat epidermal extracts are goat hides with hair intact or goat hair (in one case identified as mohair). The origin of the source material was not identified in information provided by the manufacturers.

Methods used in the manufacture of this extract are generally those used in the preparation of other epidermal extracts, but were not specified in information provided by the manufacturers.

(4) *Composition.* The composition of commercially available goat epidermal extracts as employed for diagnosis and therapy, with the exception of components of extracting and diluting fluids, is unknown. The allergens in these extracts have not been identified or characterized.

(5) *Standardization.* Goat epidermal extracts are marketed either in terms of weight per volume concentration or protein nitrogen units. There is no established standard of potency for this product, and no comparison is made of skin reactions produced by any particular batch or lot with reactions produced by a reference batch. No

information was provided on reproducibility of skin reactions with different lots of this extract. No information was provided on determination of potency by in vitro techiques. No information was provided on the stability of this product.

Refer to the general statement on standardization for further comments.

(6) *Labeling.* Currently available products are labeled "Goat", "Goat Hair", "Goat Dander", "Goat Hair (Angora)", "Goat Hair and Dander", "Goat Hair (Dairy)", and "Goat Hair (Milk)".

Refer to the general statement on labeling for further comments.

(7) *Safety.* No information was provided on the safety of goat epidermal extracts for use in diagnosis and therapy. Refer to the general statement on safety for further comments.

(8) *Effectiveness*—(i) *For diagnosis.* No information was provided by the manufacturers demonstrating the effectivenss of their extracts for the diagnosis of allergy to goats. The Panel found no reports on the use of goat epidermal extract in the diagnosis of allergy. This extract is probably not commonly used for diagnosis in current medical practice. Feinberg (Ref. 2) did state that some allergic patients, most of whom not clinically allergic to goats, had positive immediate skin test reactions to goat dander extract.

(ii) *Effectiveness for therapy.* No information was provided by the manufacturers, and the Panel found no report demonstrating the effectiveness of this extract for the treatment of allergy to goats.

(9) *Critique and conclusions.* The manufacturers provided no information, and the Panel found no information on the effectiveness and safety of goat epidermal extracts for use in diagnosis and therapy. Goat epidermal extracts prepared according to good manufacturing practices are likely to be as safe and effective for diagnosis and therapy as comparable epidermal extracts.

(10) *Recommendation.* It is recommended that goat epidermal extract be placed in Category IIIA for both skin test diagnosis and immunotherapy.

c. *Hog (Suidae)*—(1) *General description.* Hogs belong to the *Suidae* family of animals. These important farm animals are a major source of meat; their skin, hair, and other parts are used in the manufacture of many commonly encountered products (Ref. 46).

(2) *Clinical aspects.* Although farmers and animal processors may have frequent contact with hogs, allergy to these animals seems to be rare. Feinberg (Ref. 2) stated that allergy to hog hair may be due to exposure to the hair in mattresses and brushes, but it is likely that this is incorrect since processed hog hair is probably not a source of hog epithelial allergens.

(3) *Product description.* These products are available as hog epithelial, hair, or hair and dander extracts. Both aqueous and glycerinated extracts are marketed, either as weight per volume (1:5 through 1:10,000) or protein nitrogen unit (10 through 20,000 PNU per mL) solutions.

The source materials for the manufacture of hog epidermal extracts are hog hides with hair intact or hog hair. Except in one instance, the origin of the source material was not identified in information provided by the manufacturers; in that case, it was from a State university.

Methods used in the manufacture of this extract are generally those used in the preparation of other epidermal extracts.

(4) *Composition.* The composition of commercially available hog epidermal extracts as employed for diagnosis and therapy, with the exception of components of extracting and diluting fluids, is unknown. The antigens in these extracts have not been identified or characterized.

(5) *Standardization.* Hog epidermal extracts are marketed either in terms of weight per volume concentration or protein nitrogen units. There is no established standard of potency for this product, and no comparison is made of skin reactions produced by any particular batch or lot with reactions produced by a reference batch. No information was provided on the potency or the stability of this product.

Refer to the general statement on standardization for further comments.

(6) *Labeling.* Refer to the statement on labeling for general comments.

(7) *Safety.* No information was provided on the safety of hog epidermal extracts for use in diagnosis and therapy. Refer to the general statement on safety for general comments.

(8) *Effectiveness*—(i) *For diagnosis.* No information was provided by the manufacturers demonstrating the effectiveness of this extract for the diagnosis of allergy to hogs. The Panel found no reports on the use of hog epidermal extract in the diagnosis of allergy.

(ii) *Effectiveness for therapy.* No information was provided by the manufacturers, and the Panel found no report demonstrating the effectiveness of this extract for the treatment of allergy to hogs.

(9) *Critique.* The manufacturers provided no information and the Panel found no information on the effectiveness and safety of hog epidermal extracts for use in diagnosis and therapy. However, hog epidermal extracts prepared according to good manufacturing practices are likely to be as safe and effective for diagnosis and therapy as comparable epidermal extracts.

(10) *Recommendation.* It is recommended that hog epidermal extract be placed in Category IIIA for both skin test diagnosis and immunotherapy.

d. *Sheep (Ovis aries)*—(1) *General description.* Sheep are animals of the ruminant genus *Ovis*, closely related to goats. The male of the sheep is a ram, the female a ewe, the young a lamb. The skin of stillborn or very young lambs is called astrakhan or caracul. There are many varieties of wild and domestic sheep. The latter are reared for their flesh, fleece, and skin. The fleece of sheep is the principal source of wool used for making cloth. Materials made from wool are encountered in an almost endless number and variety (Ref. 46).

(2) *Clinical aspects of allergy to sheep.* Respiratory allergy to sheep epidermal allergens has been reported (Ref. 91), but was regarded as uncommon by Feinberg (Reg. 2). Except for shepherds, stockyard workers and veterinarians, proximity of humans to sheep is rare today. Unprocessed fleece may be more likely to cause allergic reactions than finished wool products. Feinberg (Ref. 2) stated that sheep wool is more likely to cause contact (skin) reactions such as urticaria or eczema than respiratory symptoms, and he believed that such reactions were due to the wool fat.

Hill (Ref. 92) stated that "wool sensitivity of such high degree that urticaria is produced by only slight contact can occur, but it is uncommon."

Fastman and Glaser (Ref. 93) tried to determine whether or not sheep wool is a cause of bronchial asthma in subjects with perennial bronchial asthma, stating that individuals with allergic rhinitis sometimes, and those with bronchial asthma less frequently, associate symptoms with exposure to wool. Using a nebulized aqueous wool extract (not further described), these investigators provoked an apparent attack of bronchial asthma in one and a questionable response in 6 of 23 asthmatic subjects by administration of 30 breaths of the extract (containing 10,000 PNU per mL). Administration of 30 breaths of a 10–fold more concentrated extract provoked asthma

in 9 and questionable asthma in 12 of 39 asthmatic subjects. Saline alone induced a positive response in one and questionable responses in 4 of 32 asthma subjects. To what degree these responses were due to nonimmunologic irritation of the lower airways is not clear. Furthermore, there was no apparent ralationship between the degree of airway responsiveness and the degree of immediate skin test response to aqueous wool extract.

There is considerable uncontrolled clinical evidence implicating wool as a cause of eczema, particularly "winter eczema" in children (Ref. 92), although sensitivity to wool is certainly not responsible for all eczema, or even all the "winter eczema."

(3) *Production description.* Review of data submitted by the manufacturers revealed that sheep wool is the source material used in the preparation of sheep epidermal extracts. The source of this material was not specified, except by one manufacturer who obtains it from the Wool Exchange. There was no description of the source material as it is used in the production of this extract.

The methods used in the manufacture of this extract were not specified by the manufacturers, and there are not data on the effectiveness of the extraction process using wool as source material.

(4) *Composition.* The Panel found no reported investigation of the composition of this extract. The allergens in wool extracts have not been identified.

(5) *Standardization.* There is no established standard of potency for sheep epidermal or wool extracts. The Panel found no report in which the potency or the stability of this extract was studied.

(6) *Labeling.* Currently available products are labeled "wool" or "sheep wool".

(7) *Safety.* The Panel found no report on the short-term or long-term safety of this extract as used in diagnosis and therapy. Hill (Ref. 92) noted a marked flareup of eczema and a lichenoid eruption in a 6-year old patient with eczema 24 hours after an injection of 0.05 mL of a 1:1,000 dilution of wool extract. Subsequent injections of 0.02 mL of a 1:10,000 dilution were well tolerated.

(8) *Effectiveness*—(i) *For diagnosis.* According to Hill (Ref. 92), positive skin test reactions to wool extract, even at high concentrations, are uncommon. He observed only 9 positive reactions in 300 eczematous infants and children. In 40 other eczematous children, scratch tests with wool extract (0.1 mg nitrogen per mL) were negative in all 40, while intracutaneous tests with the same extract were weakly positive in 10 and negative in 30. Patch tests with sections of an all-wool blanket were positive in 14, negative in 26 of these children. There was no relation between a positive patch and a positive intracutaneous test; either occurred in the absense of the other. Hill regarded the positive intracutaneous tests to be of doubtful significance; all other positive patch tests he regarded to be clinically significant in the diagnosis of eczema in these children.

Fastman and Glaser (Ref. 93) found few negative skin test reactions to wool extract in their patients. They concluded "that in patients with multiple allergic disorders including perennial asthma, the skin test for wool is of little or no value in predicting clinical sensitivity to wool." They also regarded the clincial history as of little value in predicting respiratory allergy to wool allergens.

The Panel found no documented evidence of the occurrence of IgE antibodies specific for sheep epidermal allergens or wool allergens.

(ii) *Effectiveness for therapy.* The Panel found no reports of clincial studies of sheep epidermal or wool extracts in the treatment of allergy to sheep or their wool.

Lord (Ref. 94) treated two patients who had urticaria from wool with injections of wool extract and reported excellent clinical results. Hill (Ref. 92) treated three children who had winter eczema with injections of wool extract and all three children appeared to have an excellent response, with signficantly less eczema in spite of at least minimal contact with wool.

(9) *Critique and conclusions.* Sheep may be a source of airborne allergen which can sensitize individuals who are sufficiently exposed to these ovine animals. However, it is not certain that this allergen is derived from the wool of the sheep. Wool undoubtedly aggrevates eczema, particularly in children; this may be due to wool fat and not to water-soluble epidermal allergens.

The source material used in the manufacture of sheep epidermal extracts is wool, the condition of which is not described by the manufacturer. That is, this source material might be processed prior to extraction so that the majority of relevant water-soluble allergens, if they exist, have been removed prior to extraction. The amount of these allergens in the final product is unknown and is currently not measured. Perhaps wool is not the appropriate source material for a sheep allergenic extract.

There are no data on the composition and potency of sheep wool extracts.

The manufacturers provided no data on the effectiveness and safety of their extracts for use in diagnosis and therapy. Currently available data suggest that wool extract is unsatisfactory for the diagnosis of IgE-mediated respiratory allergy to sheep epidermal allergens. It is not known whether this extract is effective for the diagnosis and treatment of urticaria or eczema due to or aggrevated by contact with wool, but the available evidence makes this seem unlikely.

The Panel suggests that an alternative source material, e.g., sheep hides or freshly clipped sheep fleece, be investigated.

(10) *Recommendations.* It is recommended that extract of wool from *Ovis aries* be placed in Category IIIB for skin test diagnosis and immunotherapy.

e. *Gerbil*—(1) *General description.* The term gerbil refers to any of the numerous burrowing rodents forming the subfamily *Gerbillinae* of the family *Cricetidae* (order *Rodentia*). There are about a dozen genera and almost 100 species of gerbils. They are found naturally in Africa and Asia. *Meriones unguiculatus*, one of the tamarisk gerbils, or jirds, is a gentle and hardy animal that became a popular pet in the United States in the mid-1960's. Gerbils and jirds are also used as research animals. They are mouselike or ratlike animals with soft pale brown or grayish fur. Adult gerbils are 10 to 15 centimeters (cm) long (Ref. 46).

(2) *Clinical aspects.* In the section on allergy to animals in standard textbooks (e.g., Ref. 47 and 95), gerbils are mentioned as an obvious source of allergen in households where these animals are kept as pets. The Panel found no other reference to clinical aspects of allergy to gerbils but it undoubtedly resembles allergy to other household pets. Allergy to gerbils probably affects some commercial breeders and laboratory workers who have contact with these animals.

(3) *Product description.* This product is listed by one manufacturer as an extract of gerbil epithelia. Both aqueous and glycerinated extracts are marketed. The source of the raw material and evidence of its identity were not mentioned in the information provided by the manufacturer. The extract is prepared from hides with hair intact which has been defatted and milled. A description of the method used in the manufacture of this specific extract was not found in the material submitted by the manufacturer.

(4) *Composition.* The Panel found no information on the composition of this

extract. Its specificity has not been studied.

(5) *Standardization.* There is no established standard of potency for gerbil epidermal extracts. The Panel found no report in which the potency or the stability of this extract was studied.

(6) *Labeling.* Refer to the general statement on labeling.

(7) *Safety.* No information was available on the safety of this extract for use in diagnosis and therapy.

(8) *Effectiveness*—(i) *For diagnosis.* The Panel found no data on the effectiveness of this extract for diagnosis of allergic disease.

(ii) *Effectiveness for therapy.* No information was provided by the manufacturer, and the Panel found no report demonstrating the effectiveness of this extract for the treatment of allergy to gerbils.

(9) *Critique and conclusions.* Allergy to gerbils probably occurs in households where these animals are kept as pets, and among laboratory workers and commercial breeders who may have more extensive contact with these animals. However, the incidence of allergy to gerbils is unknown.

The manufacturer provided no information (for example, the species from which the source material is obtained) describing the preparation of this specific extract. There is no standard of potency for this extract.

Allergy to gerbils is not common and therefore this extract is rarely used in clinical practice. As a consequence, there is inadequate information on the effectiveness and safety of gerbil epidermal extract for use in diagnosis and therapy. Nevertheless, gerbil epidermal extracts are likely to be as safe and effective as comparable epidermal extracts.

(10) *Recommendations.* It is recommended that *Gerbillus* (gerbil) epidermal extract be placed in Category IIIA for both skin test diagnosis and immunotherapy.

f. *Guinea pig*—(1) *General description.* The guinea pig is a domesticated species of South American rodent of the family *Caviidae* (Order *Rodentia*). It was domesticated in pre-Incan times and introduced into Europe in the 16th century. It is now a popular pet and a valuable research animal. Guinea pigs are stout, short legged animals about 25 cm long as adults. Their hair length and color varies (Ref. 46).

(2) *Clinical aspects.* Textbooks of allergy mention guinea pigs as relatively frequent causes of allergy in laboratory workers and occasional causes in individuals who keep them as pets (Refs. 95 through 97). Lutsky and Neuman (Ref. 7) reported that guinea pigs were the cause of the allergy in 24 percent of a group of 191 research workers with hypersensitivity to laboratory animals; this relatively high incidence probably reflects the extensive use of guinea pigs in biomedical research. The only data on the frequency of sensitivity to guinea pigs in a general group of allergic individuals are those reported by Muljono and Voorhorst (Ref. 5). They found that 9.2 percent (105 out of 1,136) of the patients visiting the Department of Allergology of the Leiden University Hospital, The Netherlands, had a distinct skin reaction to guinea pig dander extract. Only cat dander extract caused more reactions in these patients. Reactions were seen more frequently in females compared to males—62 versus 43; no explanation was given for this finding.

The clinical manifestations of allergy to guinea pigs are similar to allergy to other animals and are characteristic in laboratory workers, in whom rhinitis, conjunctivitis, cough, asthma and urticaria are typical. Continued exposure at work is said to lead to progressive involvement of the lower respiratory tract (Ref. 98).

The diagnosis of allergy to guinea pigs is usually established by a detailed clinical history. RAST has also been employed (Ref. 52).

Complete avoidance of contact with guinea pigs is the treatment of choice. Reduction of the concentration of allergens in the laboratory environment, which can be achieved in a variety of ways (Ref. 98), can reduce the intensity of symptoms. Immunotherapy is generally not recomended for the treatment of allergy to guinea pigs, but has been used occasionally; the equivocal results of therapy have not been reported.

(3) *Product description.* This product is available either as guinea pig hair or epithelial extracts. Both aqueous and glycerinated forms are marketed.

The source material is either hair or hide with hair attached. Its source and evidence of its identity were not mentioned in information provided by the manufacturers, except in one instance in which it was stated that the source material was obtained from guinea pigs in the manufacturer's own animal room.

Methods used in the manufacture of this extract are the same as those used in the preparation of other epidermal extracts; specific descriptions of the preparation of guinea pig epidermal extracts were not found in material submitted by the manufacturers.

(4) *Composition.* The composition of commercially available guinea pig epidermal extracts as employed for diagnosis and therapy, with the exception of components of extracting and diluting fluids, is unknown.

Berrens et al. (Ref. 40) obtained hair from guinea pigs by clipping their fur with an electric razor and then found that dander (obtained by washing the hair with acetone) comprised less than 1 percent (by weight) of the original sample. Of the material extractable from this dander with 1 percent NaCl solution, less than 6 percent was nondialyzable, i.e., likely to contain allergens.

Ohman et al. (Ref. 99) used fresh, unshaved guinea pig pelts as source material for the preparation of epidermal extract. The pelts were washed with water and freeze-dried. Next, they were defatted in ether, air-dried and then extracted with water for 6 hours at room temperature and overnight at 5 °C. Finally, insoluble components were removed by filtration.

They obtained 0.56 mg of nondialyzable solid per mL of a 1:10 (w/v) guinea pig pelt extract. The optical density at 280 nm of a solution of this extract containing 0.5 mg/mL nondialyzable solid was 0.54. Nine out of 9 individuals who were thought to be clinically sensitive to guinea pigs had a positive prick test to the 1:10 (w/v) pelt extract; the mean diameter of the flare response in these individuals was 13 mm. There was no apparent loss of allergenic activity on dialysis of the extract, although one individual did have a 5 mm reaction when tested with a concentrate of the dialysate. Prick test reactions to a 1:2 dilution of guinea pig serum were induced in some of the test subjects; the mean diameter of the positive reactions was 16 mm. The pelt extract was fractionated by electrophoresis in agarose gel and the allergenic activity, as assayed by prick test in individuals clinically sensitive to guinea pigs, was located in fractions with prealbumin mobility, i.e., the major allergens are acidic proteins. After filtration through a Sephadex G–100 gel column, allergenic activity was recovered in fractions containing proteins in the molecular weight range from 22,000 to 10,000 daltons. In separate experiments, rat and mouse allergens were found to be in the same molecular weight range. Ohman suggested that guinea pig pelt extract is a mixture of serum- and non-serum-derived allergenic components. Serum albumin was not one of these components.

The manufacturers provided no data on the specificity of guinea pig epidermal or hair extracts. There is no standard of potency for this product. No information is available on the stability of this product.

(5) *Standardization.* There is no established standard of potency for guinea pig epidermal extracts. The Panel found no report in which the potency or the stability of this extract was studied.

(6) *Labeling.* Refer to the general statement for labeling for comments.

(7) *Safety.* No information is available on the safety of this extract for use in diagnosis and therapy.

(8) *Effectiveness*—(i) *For diagnosis.* No information was provided by the manufacturers demonstrating the effectiveness of this extract for the diagnosis of allergy to guinea pigs. The Panel found no critical study of the question. Berrens et al. (Ref. 40) list several atopic patients who had positive skin tests to several animal dander extracts, including guinea pig dander extract, although they were not known to be clinically sensitive to guinea pigs. At the same time, the one patient listed in this report who had a positive skin test to guinea pig dander extract but not to cow, horse, dog, cat or rabbit danders, was apparently symptomatic when in contact with guinea pigs.

Sarsfield et al. (Ref. 52) did prick tests with a commercial guinea pig extract in six asthmatic children, all of whom had contact with guinea pigs but only two of whom admitted clinical sensitivity to these animals. One of the former had a minimally positive reaction (0.7 mm wheal diameter), whereas both of the latter had a positive reaction (mean wheal diameter 3.5 mm). A RAST for IgE antibody specific for guinea pig allergens was positive in only one case, one of the two with clinical sensitivity.

Muljono and Voorhorst (Ref. 5) found that allergic patients with symptoms appearing after contact with guinea pigs were very likely to have a strong skin test response to guinea pig dander extract (source not mentioned). They did observe, however, that among seven allergic patients with no complaints after exposure to guinea pigs, three had strong skin reactions to this extract.

(ii) *Effectiveness for therapy.* No information was provided by the manufacturers and the Panel found no report demonstrating the effectiveness of this extract for the treatment of allergy to guinea pigs.

(9) *Comments.* Allergy to guinea pigs occurs in households and other sites where these animals are kept as pets and among commercial breeders and laboratory workers who sometimes have extensive contact with these animals.

Little is known about the composition of guinea pig epidermal extracts.

The manufacturers provided no information, and the Panel found virtually no information on the effectiveness and safety of guinea pig epidermal extracts for use in diagnosis and therapy. As is true for other potent epidermal extracts, positive skin tests occur rather frequently in allergic individuals who are not allergic to guinea pigs. Nevetheless, this extract is as likely to be as safe and effective as comparable epidermal extracts.

(10) *Recommendations.* It is recommended that *Caviidae* (guinea pig) epidermal extract be placed in Category IIIA for both skin test diagnosis and immunotherapy. One Panel member recommends Category I for diagnosis.

g. *Hamster (Mesocricetus auratus)*—(1) *General description.* The hamster is an Old World rodent of the family *Cricetidae* (order *Rodentia*). It is a short-tailed, soft-furred animal with large cheek pouches for carrying food. There are six genera, among which is *Mesocricetus*, which includes only the golden, or Syrian, hamster (*M. auratus*). The golden hamster is a popular pet as well as a laboratory animal. It is a native of the steppe country of Asia Minor and The Balkans. All golden hamsters in captivity are apparently derived from a single litter captured in Syria in 1930. The adult animal is reddish brown with white underparts and is 15 to 20 centimeters long, including its very short tail (Ref. 46).

(2) *Clinical aspects.* Standard textbooks (Refs. 47, 95, and 97) state that pet hamsters are an occasional cause of allergy, including asthma.

In a survey of 1,293 individuals who worked with laboratory animals, Lutsky and Neuman (Ref. 7) reported that allergy to hamsters occurred in only 1.6 percent of the 191 workers who were allergic to one or more of these animals. Since the report does not indicate the number of workers who were exposed to hamsters, it is not possible to estimate the relative risk for development of this specific allergy.

The Panel found a single report describing four cases of hypersensitivity to hamsters (Ref. 100). All the patients were adults with no previous history of allergy or related respiratory disease. In each case, asthma developed after exposure to one or more pet hamsters ranging from 6 to 21 months. None of these patients had related his symptoms to contact with the pet hamster. In three cases, symptoms cleared rapidly and completely a few days after the pets were given away. In the fourth case, however, the hamster was given away, but there was no obvious improvement. The author believed that the unusually heavy concentration of hamster allergen was responsible for the persistence of illness in this patient as the patient had 15 hamsters which he allowed to wander about his small house.

(3) *Product description.* This product is available either as hamster hair or epithelial extract. Both aqueous and glycerinated extracts are marketed. The supplier of the source material and its indentity were not mentioned in the information provided by the manufacturers. One manufacturer collects hair and dander by scraping the animal's skin with a sharp blade. Further details of the manufacture of this specific extract were not found in the material submitted by the manufacturers.

(4) *Composition.* There is minimal information about the composition of hamster epidermal extract. Berrens et al. (Ref. 40) obtained hair from hamsters by clipping their fur with an electric razor and found that dander obtained by washing these clippings with acetone comprised less than 1 percent by weight of the original sample. Of the material extractable from this dander with 1 percent sodium chloride solution, less than 5 percent was nondialyzable, i.e., likely to contain allergens. The analysis was not carried further.

The Panel found no additional information on the composition of this extract.

(5) *Labeling.* Refer to the general statement on labeling for comments.

(6) *Safety.* No information is available on the safety of this extract for use in diagnosis and therapy.

(7) *Effectiveness*—(i) *For diagnosis.* The report by Wilson (Ref. 100) states that skin testing with a 2-percent extract of hamster hair by the intradermal method produced distinctly positive wheal and flare reactions in all four hamster-sensitive patients. Tests with "common allgerens" were negative, except for a small reaction to house dust extract in two of the patients.

Sarsfield et al. (Ref. 52) did prick tests with a commercial hamster extract in three asthmatic children, all of whom had contact with hamsters but only one of whom admitted clinical sensitivity to these animals. All three had a positive reaction, but the diameter of the wheal was slightly larger in the clinically sensitive child (5 mm) than it was in the other two (3 mm). In none of these children was the RAST positive for IgE antibody to hamster allergen.

The Panel found no other reports on the use of hamster epidermal extracts in diagnosis.

(ii) *Effectiveness for therapy.* No information was provided by the manufacturers, and the Panel found no report demonstrating the effectiveness of hamster extract for the treatment of allergy to hamsters.

(8) *Critique and conclusions.* Allergy to hamsters occurs in households where these animals are kept as pets and among commercial breeders and laboratory workers who sometimes have extensive contact with these animals. However, the incidence of allergy to hamsters is unknown.

The manufacturers provided no information describing the preparation of this specific extract. There is no standard of potency for this extract.

Allergy to hamsters is relatively rare. As a consequence, there is inadequate information on the effectiveness and safety of hamster epidermal extract for use in diagnosis and therapy. Nevertheless, this extract is as likely to be as safe and effective as comparable epidermal extracts.

(9) *Recommenations.* It is recommended that *Mesocricetus auratus* (hamster) epidermal extract be placed in Category IIIA for both skin test diagnosis and immunotherapy.

(h) *Mice*—(1) *General description.* Mice belong to the family *Muridae.* The common house and laboratory mouse is *Mus musculus.* Mice are rodents that live in all regions of the world. They are common inhabitants of fields, houses and barns. Mice are used extensively in biomedical research (Ref. 46).

(2) *Clinical aspects.* Lintz (Ref. 101) described the case history of a woman whose asthma was due to mice in her home. Thomas (Ref. 102) stated that mice not infrequently caused allergic symptoms but he did not document this statement. Synder and Kahan (Ref. 103) found that 60 percent of a group of 60 asthmatic children residing in an economically deprived community within New York City hatl a positive scratch test (2 plus or greater) to a commercial mouse hair extract whereas only 8 percent of a group of 60 upper middle class children seen in a private practice in the same city had a positive scratch test with the same extract. They suggested that rodent hair may act as a precipitant inhalant allergen in asthmatic children residing in a poor urban community.

Allergic reactions to mice can be a problem of considerable magnitude to laboratory personnel. Sorrell and Gottesman (Ref. 104) reported that a female research worker, after working with mice for about a year and a half, developed nasal stuffiness and sneezing whenever she worked in the room housing the mice. When scratched by a mouse, she would have a local wheal and erythema reaction with pruritis. She had no other allergies. Skin tests were positive to mouse epidermal extracts but negative to epidermal extracts of other laboratory animal pelts as well as to cat dander and dog dander. A passive skin transfer test with her serum was positive.

Arbesman et al. (Ref. 105) studied a graduate student who developed a markedly edematous forearm and severe asthma a few minutes after he was scratched on the arm by a mouse. Previously, this man had worked with mice for 2 years without difficulty. Upon reexposure to mice 3 years later he complained of rhinitis and asthma whenever he entered the room housing mice. He had a history of allergic symptoms on exposure to guinea pigs, rats, and dogs. When skin-tested, he had positive reactions to mouse pelt extract and to mouse serum. Passive skin transfer tests with this subject's serum were positive when challenged with mouse serum; the sensitizing activity of the patient's serum was heat labile. He also had positive skin tests with dander extracts and sera from many other animals.

In 10 cases of occupational allergy to laboratory animals described by Rajka (Ref. 106), three had a history of rhinitis and asthma when exposed to mice. This was confirmed by deliberate exposure of the patients to mice. All three patients had a positive skin test to an extract of mouse hair; in two cases, passive skin transfer tests were also positive. All three individuals were also allergic to one or more additional animal species.

In Lutsky and Neuman's survey of 39 animal facilities in the United States, the incidence of allergy to mice was 37 percent among 191 individuals who reported symptoms of allergy to laboratory animals. Many of these individuals were also allergic to other laboratory animals (Ref. 7).

Taylor et al. (Ref. 19) studied four laboratory workers who were allergic to mice and rats and a fifth who was allergic to rats but not to mice. The four handled both mice and rats, the fifth rats only. All gave a history of hay fever and had a positive skin reaction to one or more common allergens. Symptoms of allergy to mice appeared within 1 year after first exposure to the animals. Initial symptoms were rhinitis and conjunctivitis of rapid onset on exposure to the animals, and urticaria at sites of contact with the animals' urine. Asthma developed in all the patients, beginning within a few weeks in one case. When the patients were examined after being separated from the animals for several days, there was no clinical evidence of asthma, and pulmonary function tests were normal. All four of the patients who handled mice had immediate skin reactions to mouse hair extract, mouse urine and, in three of the four, mouse serum. Inhalation bronchial tests were positive in three subjects challenged with urine and with serum, but were negative in all four after challenge with hair extract. RAST for IgE antibodies specific for urinary allergens was positive in all four cases; three were also positive for IgE antibodies against mouse serum. Precipitin tests with the patients' whole serum were negative for antibodies against urinary and serum proteins.

(3) *Product description.* This product is available as mouse epithelial or hair extract. Both aqueous and glycerinated extracts are marketed, either as weight per volume (1:10 through 1:10,000) or protein nitrogen unit (10 through 20,000 PNU per mL) solutions.

The raw material for the manufacture of mouse epidermal extract is usually mouse pelt. It could not be determined from information provided by the manufacturers whether mouse hair is also used as source material. The origin of this material was not identified in information provided by the manufacturers, except where it was obtained from mice in one manufacturer's own animal room and in another instance from an unnamed commercial supplier.

Methods used in the manufacture of this extract are the same as those used in the preparation of other epidermal extracts; specific descriptions of the preparation of mouse epidermal extracts were not found in material submitted by the manufacturers.

Snyder and Kahan (Ref. 103) described in general terms the preparation of mouse hair extract. The hair (sic) was first defatted with petroleum ether then extracted on a weight per volume basis with buffered saline for 24 hours at 5 °C. Hairs were removed by filtration, and the extract was dialyzed and then sterilized by filtration.

Ohman et al. (Ref. 99) used fresh, unshaved mouse pelts as source material for the preparation of an epidermal extract. These pelts were washed with water and then freeze-dried. Next they were defatted in ether, air dried, and then extracted with water for 6 hours at room temperature and overnight at 5 °C. The ratio of the pelt weight to solvent volume was not given.

Finally, insoluble components were removed by filtration.

Taylor et al. (Ref. 19) used hair shaved from mice in the preparation of their extract. The hair was defatted in ether, extracted in Coca's solution (time and temperature not specified), Seitz filtered, dialyzed against distilled water, and freeze-dried.

Siraganian and Sandberg (Ref. 107) prepared an extract by freezing 30 mouse pelts, scraping them free of subcutaneous fat and connective tissue, and homogenizing them in phosphate buffered saline (pH 7.2) containing 0.01M ethylenediaminetetraacetic acid. The volume of extracting fluid used was not stated. The homogenate was stirred overnight at 4 °C, then centrifuged to remove solids. The supernatant, containing 3.14 mg protein per mL, after dialysis against phosphate buffered saline, was designated "crude mouse dander" extract.

(4) *Composition.* The composition of commercially available mouse epidermal extracts as employed for diagnosis and therapy, with the exception of components of extracting and diluting fluids, is unknown.

Levy (Ref. 25) reported that commercial mouse skin extracts contained from 0.8 to 3.4 mg trichloroacetic acid-precipitable protein per ml. In three of these extracts, mouse serum albumin comprised slightly more than half the total protein.

Ohman et al. (Ref. 99) fractionated their mouse pelt extract on a Sephadex G-100 gel column and found a major allergen in fractions containing proteins with molecular weights ranging from 10,000 to 25,000 daltons. After electrophoresis in agarose gel at pH 8.2, allergenic activity was detected (by skin test response in mouse-sensitive subjects) in fractions with the mobility of serum albumin. Mouse serum induced immediate skin reactions in many but not in all subjects allergic to mice. These investigators concluded that mouse pelt extracts are mixtures of serum and nonserum derived allergenic components.

Taylor et al. (Ref. 19) studied the allergens in mouse urine, serum and hair extract. Proteins in dialyzed mouse urine were concentrated by lyophilization and then fractionated on Sephadex G–100. Four mousesensitive laboratory workers had positive skin reactions to comparable concentrations (0.01 to 1 mg per mL) of the whole urine preparation and the Sphadex "fraction 3." This fraction contained a large amount of low molecular weight (approximately 12,400 daltons) protein which the authors identified as a prealbumin by agarose gel electroporesis. This low molecular weight prealbumin constituted more than 90 percent of the protein in the mouse urine. They were unable to detect this protein in mouse serum (by crossed immunoelectrophoresis) although others have reported that it is present in serum in very low concentration (Ref. 108).

Siraganian and Sandberg (Ref. 107) fractionated their mouse skin extract and found two major allergens. The larger of the two had a molecular weight of approximately 67,000 daltons and by biochemical and immunochemical criteria appeared to be identical to mouse serum albumin. The smaller allergen had a molecular weight of approximately 17,000 daltons; it was not further identified in this study. Both the large and small allergens were also found in mouse serum and mouse urine. The sensitivity of the leukocytes of 14 patients to these two pelt-derived allergenic fractions was examined. Four (20 percent) were clearly reactive to the larger allergen and 6 (43 percent) to the smaller allergen. The leukocytes from these 10 individuals also reacted to high concentrations of the alergen to which they were not principally reactive. Whether this was due to true reactivity to both proteins or to cross-contamination could not be determined. The cells from 4 additonal donors reacted about equally to both allergens. The authors pointed out the importance of using a number of test subjects when assaying the activity of allergenic fractions separated from crude extracts.

Mice and rats belong to the family *Muridae*, genus *Mus*. The Panel found no report in which the possibility of cross-reactivity between mouse and rat epidermal extracts was examined. Taylor et al. (Ref. 19) did mention that one of their subjects who was allergic to rats but not to mice did not react to mouse urinary and serum allergens. Nevertheless, mice or rats are sufficiently close phylogenetically to expect that some rat proteins may cross-react with corresponding mouse proteins.

The Panel found no report in which mouse pelt extract was compared with mouse hair extract.

(5) *Standardization.* Mouse epidermal extracts are marketed either in terms of weight by volume or protein nitrogen units. There is no established standard of potency for this product and no comparison is made with a reference preparation. No information was provided on the potency or the stability of this product.

Refer to the general statement on standardization.

(6) *Labeling.* Refer to the general statement on labeling.

(7) *Safety.* No information was provided on the safety of mouse epidermal extracts for use in diagnosis and therapy. Refer to the general statement on safety.

(8) *Effectiveness*—(i) *For diagnosis.* No information was provided by the manufactureres demonstrating the effectiveness of this extract for the diagnosis of allergy to mice.

In Sorrell and Gottesman's report (Ref. 104), the mouse-sensitive patient had positive skin test reactions to a commercial extract and several mouse dander extracts prepared by the authors, with a dose-related response to the latter. A control (not further specified) test was negative. The potency of these extracts was not specified.

Snyder and Kahan (Ref. 103) did skin tests with mouse hair extract prepared by Center Laboratories. Two groups were studied: Group I consisted of 210 asthmatic children; Group II consisted of 60 nonasthmatic siblings of the children in Group I. Among a subset of Group I consisting of 60 children living in a poor urban community, 86 percent had a positive skin test. The rate was lower in three other subsets of Group I children living in better urban housing. The reaction rate was 15 percent in nonasthmatic siblings (Group II). No information was provided about the relationship between skin test results and clinical evidence of allergy to mice among these children. The children reacted with approximately the same frequency to rat hair extract as they did to mouse hair extract. The potency of these extracts was not specified.

While various mouse pelt extracts induce positive skin tests and, in some cases, in vitro histamine release in a dose-related manner as reported by Levy (Ref. 25), Ohman et al. (Ref. 99) and Siraganian and Sandberg (Ref. 107), in none of these studies was the potency of the extract established, nor was the specificity of the extract for the diagnosis of allergy to mice established in a population of mouse-sensitive subjects and appropriate control subjects. The Panel found no report considering the cross-reactions between mouse and rat epidermal extracts.

(ii) *Effectiveness for therapy.* No information was provided by the manufacturers, and the Panel found no report demonstrating the effectiveness of this extract for the treatment of allergy to mice.

Sorrel and Gottesman (Ref. 104) treated their mouse-sensitive patient with mouse dander extract which they had prepared, and they reported that the patient showed "considerable

improvement" after 2 months of treatment. The maximum dose was 0.1 mL of a 1:10 dilution of the extract, the potency of which was not determined.

Wahn and Siraganian (Ref. 109) measured blocking antibody levels (as antigen neutralizing capacity of the patients' sera) in four mouse-sensitive laboratory workers who had received immunotherapy with commercial mouse skin extract for over 12 months. All the sera contained significant levels of blocking antibody activity when compared to a control serum from a nonallergic individual. Clinical evidence of effectiveness of the therapy was not obtained in this study nor did the authors study the effect of therapy on specific IgE antibody levels.

(9) *Critique and conclusions.* The manufacturers provided no information specifically describing the preparation of mouse epidermal extracts. Their composition has recently been examined but the identity of the major allergen has not been established; it may be a urinary protein. There is no established standard of potency for this extract.

The manufacturers provided no information and the Panel found insufficient information on the effectiveness and safety of mouse epidermal extracts for use in diagnosis and therapy. Nevertheless, mouse epidermal extracts are likely to be as safe and effective for diagnosis as comparable epidermal extracts, with the question of cross-reactivity with rat epidermal allergens remaining to be answered. Because some mouse epidermal extracts have been found to contain a relatively large amount of mouse albumin (Ref. 25), their use in therapy theoretically might entail more risk than most other allergenic extracts. Their safety, therefore, should be investigated carefully.

(10) *Recommendations.* It is recommended that *Mus musculus* (mouse) epidermal extract be placed in Category IIIA for both skin test diagnosis and immunotherapy. One panel member recommends Category I for diagnosis.

i. *Rabbit (Oryctolagus cuniculus)*—(1) *General description.* The rabbit is a small, gnawing animal of the family *Leporidae* (order *Lagomorpha*). Rabbits are native to Europe, Asia, Africa, and the New World. They are classed in several genera, the best known being *Oryctolagus*, which includes the Old World rabbit, *O. cuniculus* and *Sylvilagus*. *Sylvilagus* includes about 13 species of cottontail rabbits. Rabbits are long-eared, short-tailed animals with long hind-legs, being 25 to 45 centimeters (cm) long and weighing up to 7 kilograms (kg). Domestic rabbits, of which about 30 breeds and almost 80 varieties are recognized in America, are kept as pets and as show, fur, meat, and laboratory animals. The New Zealand (an Old World rabbit) is the breed most widely used in this country. The Angora rabbit is the wool-bearing cousin of the fur breeds (Ref. 46).

(2) *Clinical aspects of allergy to rabbits.* Sensitivity to rabbit was first noted in the medical literature more than a hundred years ago by Blackley (Ref. 110), who described a man in whom contact with a rabbit provoked an attack of asthma. When this man ate rabbit meat, he would develop angioedema and a gastrointestinal disturbance. Rabbits were recognized as a cause of allergic rhinitis in laboratory workers as early as 1920 (Ref. 111). In 1967–1968, 613,000 rabbits were used in biomedical research in this country (Ref. 8).

Coca et al. (Ref. 71) summarized the early literature on the various possibilities for contact with rabbit in the environment. At that time (1931), rabbit hair was used extensively in home furnishings and clothing. For example, it was used for stuffing bedding and upholstery, particularly in the homes of poor people. Among children of New York's East Side, sensitivity to rabbit hair was said to occur in one-third to one-half, while in Oklahoma where, presumably, rabbit hair was not in the furniture, only 2 percent reacted to it. Rabbit hair was a staple of the fur industry, both rabbits and hares being used interchangeably by furriers. Rabbit fur was often substituted for the furs of the beaver, fox, leopard, mink, mole, nutria, sable, squirrel and seal; and then sold under an even longer list of trade names (listed in Ref. 2). These furs were used to make all sorts of clothing, hats, rugs, etc. Felt, made of rabbit hair, was used to make hats, sounding hammers of pianos, insulation, cartridge washers and polishing pads, among other things. However, according to Feinberg (Ref. 2), it is doubtful whether finished felts are allergenic. Since rabbit hair is no longer used as widely as it was 50 years ago, the likelihood of contact is now much less.

Rynes (Ref. 3) skin tested 2,829 allergic patients in Philadelphia with a variety of animal dander extracts of unstated potency and reported that 51 out of 2,530 (2 percent) of those tested with rabbit dander extract gave a positive reaction. Only two of these patients were aware of contact with rabbits or their poducts, and only one of these two had clinical complaints upon contact with rabbits. Whether contact provoked symptoms in the other 49 patients was not noted by Rynes.

Feinberg (Ref. 2) stated that 7 percent of his private patients had positive skin tests to rabbit dander extract.

Rajka (Ref. 106) found five rabbit-sensitive cases out of 10 research workers allergic to laboratory animals. All five of his cases had nasal symptoms when in contact with rabbits. Contact also provoked asthma in two cases.

In their survey of allergy to laboratory animals among research workers in the United States, Lutsky and Neuman (Ref. 7) found that rabbits were the cause of hypersensitivity in 37 percent of the 191 affected individuals.

Muljono and Voorhorst (Ref. 5) found a distinctly positive skin reaction to rabbit dander extract in 69 (6.1 percent) of the 1,136 allergic patients tested in their allergy clinic; of these, 30 were males, 39 females. Sensitivity was most frequent in individuals between 21 and 30 years of age.

(3) *Product description.* This product is available as rabbit hair, dander, or epithelial extracts. Both aqueous and glycerinated forms are marketed.

The source material is unsually hair or hide with hair attached; dander (not further described) is also used. The origin of the source material and evidence of its specific identity were not described in the information provided by the manufacturers; only in one instance, it was stated that the source material was obtained from rabbits in the manufactuer's own animal room.

Methods used in the manufacture of this extract are the same as those used in the preparation of other epidermal extracts; specific descriptions of the preparation of rabbit epidermal extracts were not found in material submitted by the manufacturers except for one manufacturer who provided a general description of the collection and preextraction processing of hair and dander from rabbits and other small mammals.

Ohman et al. (Ref. 99) described the method they used to prepare a potent rabbit pelt extract. Four or more fresh, unshaved rabbit pelts were washed with water and then lyophilized for 72 hours. Next they were defatted with ether, air-dried and then extracted with water (1:10 w/v) at room temperature for 6 hours, then overnight at 5 °C. After adjusting the pH to 7.5 with 0.1 N NaOH, the aqueous phase was separated from pieces of pelt by pressing through Dacron gauze. The extract was then filtered to remove insoluble components. Aliquots of this crude extract were then lyophilized and stored under sterile conditions at 5 °C.

(4) *Composition.* The composition of commercially available rabbit epidermal extracts as employed for diagnosis and therapy, with the exception of components of extracting and diluting fluids, is unknown.

Berrens et al. (Ref. 40) obtained hair from rabbits by clipping their fur with an electric razor and then found that dander obtained by washing the clippings with acetone comprised about 1 percent by weight of the original sample. Of the material extractable from this dander with 1 percent NaCl solution, less than 6 percent (53 mg per gram of dander) was nondialyzable, i.e., likely to contain allergens. The total hexose content of this extract was 4.4 percent.

Ohman et al. (Ref. 99) obtained 0.98 mg of nondialyzable solid per ml of 1:10 (w/v) rabbit pelt extract. The optical density at 280 nm of a solution of this extract containing 0.5 mg/ml (nondislyzable solid) was 0.57. Seven out of eitght individuals who were thought to be clinically sensitive to rabbit had a positive prick test to the 1:10 (w/v) pelt extract. The mean diameter of the flare response in these individuals was 18 mm. Seven of these individuals were skin tested with dialyzable solid from the crude pelt extract and with a 1:2 dilution of rabbit serum; none reacted. The pelt extract was fractionated in agarose gel electrophoresis and most of the allergenic activity, as assayed by prick test in five individuals clinically sensitive to rabbits, was located in fractions with the mobility of albumin, i.e., the major allergens are acidic proteins. After filtration on a Sephadex G–100 gel column, allergenic activity was recovered in fractions containing proteins in the molecular wight range from 38,000 to 18,000 daltons. This was somewhat larger than the size range for the major rodent pelt allergens reported by the some investigators.

The Panel found no report in which rabbit pelt extract, rabbit hair extract and rabbit dander extract were compared. There were no reports on the composition of extracts of various furs made from rabbit pelts. The manufacturers provided no data on the specificity of rabbit epidermal extracts.

(5) *Standardization.* There is no established standard of potency for this product. No information is available on its stability or potency.

(6) *Labeling.* Refer to the general statement on labeling.

(7) *Safety.* No information is available on the safety of this product for use in diagnosis and therapy.

(8) *Effectiveness*—(i) *For diagnosis.* No information was provided by the manufacturers demonstrating the effectiveness of this extract for the diagnosis of allergy to rabbits. The Panel found no critical study of the question. Sevenal reports do provide data no the frequency of positive skin reactions to unstandardized rabbit epidermal extracts (cited above). In the study by Muljono and Voorhorst (Ref. 5), allergic patients with symptoms appearing after contact with rabbits were very likely to have a strong skin test response to rabbit dander extract. However, 6 out of 17 patients having no symptoms upon exposure to rabbits nevertheless had strong skin reactions to this extract.

Sarsfield et al. (Ref. 54) did prick tests with a commerical rabbit epidermal extract in nine asthmatic children, all of whom had contact with rabbits but only four of whom admitted clinical sensitivity to these animals. All nine had a positive reaction; the mean wheal diameter of reactions in both symptomatic and asymptomatic patients was 3.8 mm. A RAST for IgE antibody specific for rabbit allergens was positive in three of the four symptomatic patients while it was negative in all five of the patients with no admitted clinical sensitivities.

One manufacturer reported that 64 of 186 patients (34 percent) tested with their rabbit hair extract over a 3 month period had a positive skin reaction.

(i) *Effectiveness for therapy.* No information was provided by the manufacturers demonstrating the effectiveness of this extract for the treatment of allergy to rabbits.

Rajka (Raf. 106) gave immunotherapy, with an aqueous extract of rabbit hair, to three rabbit-sensitive laboratory workers. The results of this therapy were said to be equivocal.

Brown and Wolfe (Ref. 56) mention that one rabbit-sensitive laboratory technician was treated with pyridine-extracted, alum-precipitated rabbit epidermal extract. This patient could not tolerate more than 1,000 PNU of this extract per injection; 1,500 PNU induced an attack of asthma. The patient's symptoms, mainly asthma upon exposure to rabbits, did not improve during the course of therapy.

The Panel found no other reports describing the results of therapy with rabbit epidermal extract.

(9) *Critique and conclusions.* Allergy to rabbits occurs in households and other sites where these animals are kept as pets and among commercial breeders and laboratory workers who sometimes have extensive contact with these animals. Allergy may have occurred previously as a consequence of the use of rabbit hair in a variety of household items, but this possibility was never clearly established and may no longer be important. The likelihood of allegy to rabbit hair and pelts which have been processed for use in clothing, furniture, etc., is probably very remote.

Little is known about the composition of rabbit epidermal extracts.

The manufacturers provided no information, and the Panel found little information, on the effectiveness and safety of rabbit epidermal extracts for use in diagnosis and therapy. Nevertheless, this extract is likely to be as safe and effective as comparable epidermal extracts. In general, immunotherapy is not recommended for this allergy.

(10) *Recommendations.* It is recommended that *Oryctolagus cuniculus* (rabbit) epidermal extract be placed in Category IIIA for both skin test diagnosis and immunotherapy. One Panel member recommended Category I for diagnosis.

j. *Rat (Rattus)*—(1) *General description.* The term "rat" refers to any of the more than 500 named forms of the genus *Rattus*, family *Muridae* (order *rodentia*). Ordinarily "rat" refers to either the black rat (*R. rattus*) or the brown Norway rat (*R. norvegicus*). Rats are ubiquitous, the Norwegian being the most abundant. Domesticated albino strains of *R. norvegicus* are commonly employed in laboratory research (Ref. 46).

(2) *Clinical aspects of allergy to rats.* In various textbooks of allergy, allergy to rats is mentioned as an occasional cause of allergic rhinitis, asthma and urticaria. Laboratory workers appear to be at greatest risk. Tuft (Ref. 112) said that individuals who live in homes or who frequently visit buildings infested with rats occasionally become allergic to these rodents. Since rat pelts are not used commerically, the only possible source of contact would seem to be a direct one, although the source itself may be hidden.

When Romanoff reviewed the literature in 1940, he could find no reports of sensitivity to rats (Ref. 113). He then described the case of a laboratory technician who suffered typical allergic rhinitis and conjunctivitis when working near rats, and urticaria of her hands whenever she handled these animals. The diagnosis was substantiated by a positive skin reaction to rat epidermal extract, and the prompt appearance of symptoms upon deliberate exposure to rats.

Gilday (Ref. 114) reported the case of a rat-sensitive veterinarian who had a systemic anaphylactic reaction with dyspnea, cough and wheezing 30

seconds after an intracutaneous test with a 1:1,000,000 dilution of stock rat hair extract. The symptoms responded promptly to two doses of epinephrine.

Among 10 cases of occupational allergy to laboratory animals described by Rajka (Ref. 106), three had a history of allergic rhinitis, and one also had asthma when working with rats. Two persons also had urticaria when they handled rats. A diagnostic exposure test was positive in all three cases, as were the skin tests with rat hair extract. Passive skin transfer tests were negative in two cases and not done in the third.

Synder and Kahan (Ref. 103) found a total of 94 positive scratch test reactions among 210 asthamatic children living in or near New York City. These children and the nonasthmatic siblings of some of them were seen in several allergy clinics and a private practice, and the children from the poorest community were found to have a significantly higher frequency of sensitivity to rat hair extracts than children from other neighborhoods. The incidence of positive reactions was 80 percent in children from an economically deprived community, whereas it was only 18 percent in those children from an upper middle class neighborhood. Furthermore, among their respective siblings, 17 percent and 0 percent has a positive reaction to rat hair extract.

Frankland (Ref. 115) described a laboratory worker who became allergic to rats after working in the laboratory for 3 years. In addition, he noted that in 42 rat-allergfic patients, clinical symptoms included local urticaria in 34 (81 percent), allergic rhinitis in 35 (83 percent) and asthma in 20 (48 percent).

In their survey, Lutsky and Neuman (Ref. 7) found that rats were the most frequently reported cause of allergy among laboratory workers, being present in 108 of 191 (56.5 percent) cases. Perhaps the abundance of these animals in biomedical research facilities contributed to this finding.

Taylor et al. (Ref. 19) studies five laboratory workers who were allergic to rats. All gave a history of hay fever and had a positive skin reaction to one or more common allergens. Positive skin reactions to rat hair extract were observed in all five subjects.

(3) *Product description.* This product is available as rat epithelial or hair extract. Both aqueous and glycerinated extracts are marketed, either as weight-per-volume (1:10 through 1:10,000) or protein-nitrogen solutions (10 through 20,000 PNU per mL) solutions.

The source material for the manufacture of rat epidermal extract is usually rat pelt. It could not be determined from information provided by the manufacturers whether rat hair is also used as source material. The origin of the source material and evidence of its identity were not mentioned in information provided by the manufacturers except that in one instance it was stated that it was obtained from rats in this manufacturer's own animal room.

Methods used in the manufacture of this extract are the same as those used in the preparation of other epidermal extracts; specific description of its preparation were not found in material submitted by the manufacturers.

A detailed description of the preparation of rat depilated whole skin powder and powdered rat epidermis is given in Reference 116.

Snyder and Kahan (Ref. 103) described the preparation of commercial rat hire extract. The hair (sic) was first defatted with petroleum ether then extracted on a weight-per-volume basis with buffered saline for 24 hours at 5 °C. Hairs were removed by filtration, and the extract was dialyzed, then sterilized by filtration.

Ohman et al. (Ref. 99) used fresh, unshaved rat pelts as source material for the preparation of their epidermal extract. These pelts were washed with water and then freeze-dried. Next they were defatted in ether, air dried and then extracted with water (ratio of pelt weight to solvent volume not given) for 6 hours at room temperature and overnight at 5 °C. Finally, insoluble components were removed by filtration.

Taylor et al. (Ref. 19) used hair shaved from rats in the preparation of their extract. The hair was defatted in ether, extracted in Coca's solution (time and temperature not specified), Seitz filtered, dialyzed against distilled water, and freeze-dried.

(4) *Composition.* The composition of commercially available rat epidermal extracts as employed for diagnosis and therapy, with the exception of components of extracting and diluting fluids, is unknown.

Ohman et al. (Ref. 99) fractionated their rat pelt extract on Sephadex G–100 and found the major allergenic activity in fractions with an approximate molecular weight of 20,000 daltons. After electrophoresis in agarose gel at pH 8.2, allergenic activity was recovered from a broad region of the gel-containing proteins with mobilities ranging from that of albumin to that of an alpha-l-protein; maximum activity was recovered in fractions with the mobility of albumin. Prick test reactions to rat serum were obtained in some, but not all, subjects who responded to the pelt extract. These investigators concluded that rat pelt extracts contain mixtures of serum- and nonserum-derived allergenic components.

Taylor et al. (Ref. 19) studied the allergens in rat urine, serum, and hair extract. Five atopic laboratory workers with allergy to rats and mice were used in the examination of the allergenic activity of a whole-urine preparation and fractions thereof, serum and hair extract. All five subjects had skin and bronchial challenge reactions to whole-urine. Proteins in dialyzed rat urine were concentrated by lyophylization and then fractionated on Sephadex G–100. The principal allergen was found in "fraction 3," which contained the urine-specific alpha-2-globulin but no serum-derived components. The proteins in this fraction are of low molecular weight (10,000–25,000 daltons), and they are not demonstrable in rat serum by crossed immunoelectrophoresis. In general sensitivity to urinary proteins appeared to be greater than to hair extract or serum. These investigators concluded that rat urine is an important source of allergenic protein.

The Panel found no report in which rat pelt extract was compared with rat hair extract. Since rats and mice belong to the same family, they may be sufficiently close phylogenetically to expect that some rat proteins may cross-react with the corresponding mouse proteins. The Panel found no report in which this possibility was examined critically. Taylor et al. (Ref. 19) found that one of their subjects, who was allergic to rats but not to mice, did not react to mouse urinary and serum allergens.

(5) *Standardization.* Rat epidermal extracts are marketed in terms of either weight per volume or PNU. There is no established standard of potency for this product and no comparison is made with a reference preparation. No information was provided on the potency or the stability of this product.

(6) *Labeling.* Refer to the general statement on labeling.

(7) *Safety.* No information was available on the safety of rat epidermal extracts for use in diagnosis and therapy.

(8) *Effectiveness*—(i) *For diagnosis.* No information was provided by the manufacturers demonstrating the effectiveness of this extract for the diagnosis of allergy to rats. The Panel found no critical study of this question. While various rat hair or pelt extracts did induce positive skin tests in individuals who were known to have clinically significant allergy to rats, with negative reactions being observed in allergic and nonallergic controls (Refs. 103 and 115), in none of these studies

was the potency of the test material established, nor was the specificity of the extract for the diagnosis of allergy to rats established in a population of rat-sensitive subjects and appropriate controls.

(ii) *Effectiveness for therapy.* No information was provided by the manufacturers and the Panel found no report demonstrating the effectiveness of this extract for the treatment of allergy to rats.

Gilday (Ref. 114) reported that injections of a stock rat hair extract were given to a 38 year old veterinarian who used rats in his research work, and complete disappearance of the patient's asthma followed. No details of the treatment were given.

Rajka (Ref. 106) reported that one of this patients had a "good effect" as a result of treatment for rat allergy; no details were given.

Wahn and Siraganian (Ref. 109) measured blocking antibody levels (as antigen neutralizing capacity of the patients' sera) in six rat-sensitive laboratory workers who had received immunotherapy with a commercial rat skin extract for over 12 months. All the sera contained significant levels of blocking antibody activity. Clinical evidence of effectiveness of therapy was not obtained in this study nor did the authors study the effect of therapy on specific IgE antibody levels.

(9) *Critique and conclusions.* The manufacturers provided no information specifically describing the preparation of rat epidermal extracts. Their composition has recently been examined but the major allergen has not yet been identified; it may be a urinary protein. There is no standard of potency for this extract.

The manufacturers provided no information and the Panel found insufficient information on the effectiveness and safety of rat epidermal extracts for use in diagnosis and therapy. Nevertheless, rat epidermal extracts are likely to be as safe and effective for diagnosis as comparable epidermal extracts, with the question of cross-reactivitiy with mouse epidermal allergens remaining to be answered.

(10) *Recommendations.* It is recommended that *Rattus rattus* and *R. norvegicus* (rat) epidermal extracts be placed in Category IIIA for both skin test diagnosis and immunotherapy. One Panel member recommended Category I for diagnosis.

6. *Allergenic extracts derived from miscellaneous mammalian epidermal sources.* Extracts of each of the following materials are listed by one or more of the licensed manufacturers. Allergy to some of them, and perhaps to other mammalian epidermal allergens, undoubtedly occurs in isolated instances. The Panel decided that when any of them is produced for clinical use, it should be handled as recommended for "Miscellaneous Inhalant Allergenic Extracts."

Each of these extracts is considered briefly below. The following general comments pertain to all of them unless otherwise noted. The manufacturers provided no description of the source materials, nor was the method used in their preparation specified. The Panel found no information on the composition, safety, and effectiveness for diagnosis and therapy of any of them.

It is recommended that allergenic extracts derived from these miscellaneous mammalian sources be placed in Category IIIA for both skin test diagnosis and therapy, except as recommended otherwise below. Those extracts described as "wool" which are prepared from processed hairs are recommended for Category IIIB.

a. *Angora.* See the earlier discussion on goat extracts.

b. *Camel (Camelus bactrianus).* Camel hair is obtained from the Bactrian (two-humped) camel and used alone or with sheep's wool in the production of camel cloth, dress goods, shawls, blankets, rugs, hats, brushes, etc. Camel hair is regarded as an allergen, although it rarely causes allergy (Refs. 74 and 98), particularly if it has been processed for commercial use. Extracts of camel hair and or camel epithelium are available.

c. *Cashmere.* See the earlier discussion on goat extracts.

d. *Chamois.* Chamois is the tanned hide of *Rupicapra rupicapra.* The tanning of hides generally destroys or removes the dander or other allergens responsible for most human sensitivity to other animal hides. The Panel found no evidence that the tanned chamois skin was allergenic. Therefore, it recommends that extracts of chamois skin be placed in Category IIIB for diagnosis and therapy.

e. *Chihuahua.* See the earlier discussion on dog extracts.

f. *Deer.* Members of the family *Cervidae* (order *Artiodactyla*), deer exist in about 16 genera and 40 species. They are hunted for meat, hides and antlers. Contact with stuffed deer head has been reported to cause allergy (Ref. 74). Whether this represents hypersensitivity to allergens derived from the deer has not been proven.

g. *French poodle.* See the earlier discussion on dog extracts.

h. *Human dander*—(1) *Introduction.* It has been estimated that an adult person sheds about 5 grams of dander (derived from the stratum corneum of the epidermis) per week. Human dander is a major component of the airborne particulate matter in the indoor environment (Ref. 14), and a significant amount of it is deposited in the environment of the home (Ref. 117). Storm Van Leeuwen et al. (Ref. 118) were among the first to suggest that human skin is a source of allergen. Voorhorst (Ref. 119) obtained evidence that rhinitis and/or asthma in hairdressers is sometimes caused by allergy to human dander, and he cited Urbach (Ref. 120) who ascribed the coryza of barbers, hairdressers and wig makers to the human dander allergen. Still, there is a great deal of reluctance on the part of allergists to acknowledge that human skin may be a source of allergen.

Since human dander is an important component of house dust, it has been regarded by some allergists as a potential contributor to the allergenic activity of house dust. Human dander is an excellent growth medium for the house dust mite (Ref. 121) and thus may also contribute indirectly to the allergenic activity of house dust extracts. For a review of the relationship of human dander to house dust allergen, refer to the section on house dust allergenic extract.

(2) *Clinical aspects.* In this country, human dander extract has seldom been included in the routine series of skin test allergens; the opposite is (or was) true in some European clinics. For example, Storm van Leeuwen et al. (Ref. 118) found that non-atopic persons seldom showed skin reactions to this extract, whereas 90 to 95 percent of their asthmatic patients did. Voorhorst (Ref. 122) reported that 476 out of 970 allergic patients (49 percent) had a positive skin test to an extract of human dander prepared in his clinic and containing the "biologically equivalent concentration" of 10 Noon equivalent units per mL. In the same series, 30 percent of the patients reponded to *Dermatophagoides pteronys sinus* extract, 16 percent to grass pollen extract. Some patients who are sensitive to human dander also react to an extract of their own dander. Voorhorst (Ref. 122) has also obtained positive passive skin transfer (P-K) reactions with the sera of human dander-sensitive patients; and the activity of these sera was abolished by heating the sera at 56 °C for 30 minutes, i.e., there are IgE antibodies to some component in human dander extract.

It has been suggested that human dander may be a particularly important allergen in patients with atopic dermatitis (eczema). For example,

Hampton and Cooke (Ref. 123) reported positive skin test reactions to a human dander extract in the majority of a group of 33 patients with eczema. This could have been due to the generally heigthened reactivity of eczematous skin. However, positive P-K tests were elicited in normal recipients with serum from 30 of these patients. The same authors also found that atopic patients without eczema reacted less frequently than patients with eczema did and, in fact, the former group reacted to dander extract at the same rate as nonallergic controls.

(3) *Product description.* Human dander is obtained by washing human hair (cut from the head with scissors or razor) with an organic solvent or collected as debris from electric razors. It is extracted in the same manner as other animal danders. Information submitted by the manufacturers does not indicate that attention is paid to the general health of the donor whether the donor is free of skin or scalp disease and hepatitis. The possible contamination of the source material by chemicals such as dyes, soaps and denaturants is not considered either. Hampton and Cooke (Ref. 123) advocated dialysis of human dander extracts to remove nonspecific irritants which may cause false-positive reactions. Voorhorst (Ref. 122) described the preparation of an acetone-precipitated human dander extract.

(4) *Composition.* The Panel found no information on the composition of human dander extracts. Voorhorst (Ref. 122) states that both deep epidermal and keratinized epidermal cells contain the same allergen.

Simon (Ref. 124) reported that dander allergen was not detectable in material obtained from the scalp of a newborn infant and from dermoid cysts, and he suggested that an unidentified microorganism may be responsible for the allergenic activity of dander extracts. He also found no evidence for shared antigenicity between human dander and other mammalian danders (Ref. 125).

(5) *Standardization.* There is no established reference preparation for this extract. Voorhorst (Ref. 122) claims that human dander is a relatively weak allergen in man, since it contains 1,000 times less "biologically equivalent allergen units" than cat dander extract. Its potency and stability have not been studied.

(6) *Labeling.* Refer to the general comments on labeling.

(7) *Safety.* There have been no studies of the safety of this extract in diagnosis and therapy. The possibility that infectious virus may be present in human dander extract has not been ruled out.

(8) *Effectiveness*—(i) *For diagnosis.* The manufacturers provided no data on the effectiveness of their extracts to diagnose allergy to human dander. Positive skin tests have been elicited in atopic individuals by extracts of human dander. In at least one report, positive skin test reactions occurred with equal frequency in allergic and nonallergic individuals (Ref. 123). Positive skin test reactions may occur with greater frequency in patients with atopic dermatitis (Ref. 123), but human dander extract is not used in the diagnosis of that condition.

Uehara and Ofuji (Ref. 127) recently found that 66 percent of patients with atopic dermatitis will have a positive patch test reaction to human dander compared to a reaction rate of only 3 percent in individuals without dermatitis. These authors also found a strong correlation between patch test reactions and delayed intradermal skin test reactions to human dander. The meaning of these observations is not clear.

(ii) *Effectiveness for therapy.* The manufacturers provided no data, and the Panel found none on the use of human dander extracts in therapy.

(9) *Critique and conclusions.* Although human dander is undoubtedly a significant component of ambient indoor air, there is no compelling evidence for the existence of clinically significant respiratory allergy to human dander. Evidence for its existence is based on a few reports of allergic symptoms in hairdressers and barbers, on positive skin test reactions to human dander extract in atopic patients and on P–K tests with sera from patients having these reactions. Voorhorst regards allergy to human dander as the prototype of auto-allergy (Ref. 123). Nevertheless, the existence and importance of allergy to an intrinsic component of human dander remains uncertain and requires further investigation.

There is no standard way of collecting human dander and no standard way of extracting it. Attention has therefore not been paid to the health of the donor nor to the purity of the source material, particularly with regard to chemical substances which it may contain. These deficiencies must be resolved in order to produce a safe and effective human dander extract. A reference preparation must be established so that a product can be manufactured with consistent composition and potency. The safety of the product must be tested, and it must be properly labeled.

(10) *Recommendations.* It is recommended that human dander extracts be placed in Category IIIA for diagnosis and therapy. One Panel member recommended Category I for diagnosis.

i. *Leather.* Leather is skin prepared for use by tanning, or some similar process. An extract of cow and horse leather is available. According to Feinberg (Ref. 2), leather, particularly if it is old and rotting, may be allergenic. This is certainly a rare cause of allergy, and it is not certain that the allergen in leather is derived from the mammalian source itself.

j. *Mink.* Mink are either of two weasel-like species of the genus *Mustela (M. vison* or *M. lutreola)* which are trapped or raised domestically for their furs. Allergy to this animal may occur in trappers and those who raise the animal domestically (Ref. 2). An extract of mink epithelium is available.

k. *Monkey.* A monkey is any animal of the order *Primates,* except man and the lemurs. In addition to their wide distribution is the tropics, monkeys are used in medical research and sometimes kept as pets. Monkey fur is sometimes used in wearing apparel. A case of asthma related to contact with a pet monkey has been reported (Ref. 4). An extract of monkey hair is available.

l. *Pony.* See the earlier discussion on horse extracts.

m. *Poodle.* See the earlier discussion on dog extracts.

n. *Raccoon.* The raccoon is a member of the family *Procyonidae,* genus *Procyon,* of which there are two to seven species. The typical North American raccoon is *P. lotor.* Raccoons are hunted and trapped for their fur and flesh; and they exist as urban pests and occasionally as pets. Allergy to raccoons, if it occurs, must be extremely rare. An extract of raccoon epithelium is available.

o. *Sheep wool.* See the earlier discussion on sheep extracts.

p. *Other miscellaneous mammals.* A wide variety of other mammals has been cited in textbooks and their sources as causing allergic symptoms in isolated instances. For example, see Ref. 71. However, extracts of the epithelia or hair of these animals are not commercially available.

7. *Allergenic extracts derived from furs.* Extracts are listed as being derived from the following furs:

(i) Beaver (Castor canadensis).

(ii) Caracul—see sheep.

(iii) Chinchilla (*Chinchilla lanigera).*

(iv) Ermine (*Mustela erminea*).

(v) Fox, including red fox and silver fox (*Vulpes vulgaris* or *V. vulpes*).

(vi) Gerbil (*Gerbillinae*).
(vii) Kolinsky fur.
(viii) Leopard (*Leo pardus*).
(ix) Marmot (*Marmota marmota*).
(x) Mink (*Mustela vison*).
(xi) Muskrat (*Ondatra zibethica*).
(xii) Nutria (*Myopotamus coypus* or *Myocastor coypus*).
(xiii) Opossum (*Didelphys virginiana* or *D. marsupialis*).
(xiv) Persian lamb—see sheep.
(xv) Raccoon (*Procyon lotor*).
(xvi) Sable (*Hippotragus niger* or *Martes zibellina*).
(xvii) Seal (family *Pinnipedia* or *Phocidae*).
(xviii) Skunk (*Mephitis mephitica* or *M. macroura*).
(xix) Squirrel (*Sciurus vulgaris*, the red squirrel and *S. carolinensis*, the gray squirrel).

This list refers to extracts made from pelts which have been processed by a variety of physical and chemical manufacturing procedures such as cleaning, sterilizing, dyeing and other steps for use in garments.

Inexpensive fur garments are frequently made with fur from rabbits or other animals but may be sold under other names. Feinberg (Ref. 2) lists these furs with their name and original sources.

Textbooks (Refs. 3 and 96) state that furs may induce rhinitis and asthma in fur workers and dealers and, rarely, in people who wear furs. Most authors (Refs. 71 and 112) doubt that processed furs contain significant amounts of allergen. Tuft (Ref. 112) claims that individuals become allergic to the dyes and other chemicals used in processing furs rather than to the epithelium itself. These substances may cause respiratory and cutaneous allergic reactions. If sensitization to the epithelium does exist, it probably results from contract with the animal skin prior to processing.

Furs used in the preparation of these extracts are purchased from commercial sources. The method used in the preparation of these extracts was not specified by the manufacturers.

The Panel found no information on the composition of any of the above extracts. Whether these extracts contain dyes and other chemicals leached from the furs is unknown. There are no established reference standards for any of them.

The Panel found no information on the safety of any of these extracts as used in diagnosis and therapy.

The Panel found no information on the effectiveness for diagnosis or therapy of any of these extracts. There are no data on the frequency of their use in practice.

Sensitivity to allergens in unprocessed furs probably occurs infrequently in fur workers. It is not certain whether processed furs contain sufficient residual mammalian allergens to induce hypersensitivity. Allergy to such furs may be provoked in furriers and consumers by dyes and other chemicals which are used to process them. The methods of preparation of these extracts, and their composition, safety and effectiveness are not known.

The Panel recommends that extracts of processed furs be placed in Category IIIB for diagnosis and therapy.

8. *Allergenic extracts derived from feathers*—a. *General description and clinical aspects.* Feathers are the visible epidermal appendage of birds (class *Aves*). The first feathering of young birds is called "down." Feathers and down, mainly those of chicken, duck and goose, are used extensively in pillows, bed covers, cushions, upholstery and winter garments. Of course, people also have contact with feathers which are on live birds or in their immediate environment; for example, commercial poultry breeders and processors, bird fanciers, etc. Licensed products include canary, chicken, duck, goose, parakeet, parrot, pigeon, and turkey feather extracts.

It has long been known that many allergic patients, particularly those with perennial allergic rhinitis or perennial asthma, will have a positive skin test reaction to various feather extracts, and allergists have considered feathers, particularly those in bedding, to be a significant source of allergen (Ref. 95). It has also been recognized that extracts of freshly plucked feathers are often inactive in patients who react strongly to extracts of "aged" feathers (Ref. 128). Thus, the allergenic substances in feathers may be degradation products. Voorhorst (Ref. 129) believes that feather extracts exert allergenic activity on the basis of their content of house dust allergens, although other authors (Ref. 131 and 132) have presented evidence to suggest that feather and house dust allergens are not completely identical. Feather bedding may contain the mites, molds, and bacteria which are present in some house dusts so that extracts made from aged feathers probably do contain some of the same allergens found in house dust extracts.

There are case reports describing respiratory illness due to sensitivity to canaries, parakeets, parrots, pigeons, turkeys, and sparrows (see, for example (Ref. 132). However, the possibility that some of these patients may have had avain hypersensitivity pneumonitis cannot be ruled out (Ref. 95).

There is no characteristic pattern to feather allergy. In some cases of hypersensitivity to feathers, the patients can sleep on feather pillows without symptoms but have attacks of sneezing when making their beds. Occasionally, attacks are induced only to the contents of the patient's own pillows (Ref. 133). Some patients are said to manifest their allergy to the contents of their pillows only when the humidity is high, suggesting that the allergens are resulting from the growth of molds, bacteria, or mites in the pillows. It is of interest that feather-sensitive patients can eat meat of the same birds without provoking an allergic reaction and feather-sensitive patients do not experience allergic reactions to eggs or egg-containing vaccines unless they have a concomitant allergy to egg proteins (Ref. 95).

The frequency of clinically significant allergy to feathers in allergic patients is unknown. All of the information on the frequency of sensitivity to feathers is derived from reports to skin test reactions to various undefined feather extracts. For example, Balyeat (Ref. 96) skin tested 100 asthmatic children under 14 years of age and found 41 percent with a positive reaction to chicken feather extract, 33 percent reactive to goose feather extract, 31 percent reactive to duck feather extract, and 26 percent reactive to all three extracts. The test concentrations used were not mentioned. Balyeat regarded feathers as the sole cause of the asthma in 16 percent of these children.

Halpin and Prince (Ref. 130) reported 315 (67 percent) positive reactions to a mixed feather dust extract in 469 house dust-sensitive patients skin tested by eight allergists. No test concentrations were mentioned.

Barr and Sherman (Ref. 132) performed skin tests on 59 allergic individuals known to have a positive skin test reaction to mixed feather extract. Forty-one persons had a positive reaction to parakeet feather extract, and 18 persons' reactions were negative. Twenty-three had a positive reaction and 12 had a negative reaction to canary feather extract. In all cases, the reaction to the mixed feather extract was stronger than the reaction to the other two. The same authors found six out of seven passive serum transfer tests with the feather extract to be positive. Serum of only one patient gave an unequivocally positive reaction with parakeet feather extract.

One manufacturer reported to the Panel that 13.8 percent of 94 allergic individuals had a positive skin test reaction to a 1:10 (w/v) extract of chicken feathers. None of 34 nonallergic control patients reacted to the same extract at this strength (Ref. 126.)

Various feather extracts induce positive skin test reactions in patients who are clinically sensitive to birds kept as pets in their homes (for example, see Ref. 132).

Feather extracts have been used extensively in the treatment of patients with allergic symptoms and a positive skin test reaction to one or more of these extracts. However, removal of the feathers from the patient's environment is regarded as essential for effective control of the patient's symptoms (Ref. 96).

b. *Product description.* Aqueous and glycerinated extracts of the above listed feathers, as well as mixtures derived from two or more species of feathers, are currently listed. the exact nature of the source materials used in the preparation of these extracts was not provided to the Panel in the information given by the manufacturers. In one instance, The source material was mixed feathers from used feather-stuffed pillows; no attempt was made to identify the source as chicken, duck or goose since the manufacturer believes that the allergenicity of the three types of feathers is the same. This same manufacturer removes any feathers which have been dyed from the source material, as well as other foreign material which may be present, before extraction.

Methods used in the manufacture of these extracts appear to be similar to those used in the preparation of other epidermal extracts.

Berrens (Ref. 131) prepared an extract of mixed feathers from the fillings of a mattress which was at least 40 old. Macroscopically, these feathers appeared to be considerably decomposed. The material consisted of brownish-black degenerated feather residue. The barbs, tachis, and even the quills had become brittle and had disintegrated almost completely. The material was not defatted but was simply extracted directly with an aqueous buffer solution. Possible contamination with mold, mites and other organisms was disregarded. Berrens extracted 750 g of the disintegrated feathers with 6 liters of 1 percent NaC1 solution with vigorous stirring for 6 hours at room temperature. The extracting fluid contained 1 percent phenol as a antibacterial and wetting agent. After extraction, the mixture was filtered to yield a clear, deep brown extract. The composition of this extract is described below.

c. *Composition.* The Composition of commercially available feather extracts as employed for diagnosis and therapy, with the exception of the extracting and diluting fluids, is unknown.

Berrens' extract (Ref. 131) contained about 2.5 percent of water-soluble material. An exact value could not be fixed since its protein content could not be determined by absorption spectroscopy or by means of the biuret reaction. The sample was dialyzed and then lyophilized. The resulting brown powder represented 0.5 percent (by weight) of the starting raw material. This nondialyzable material dissolved readily in water. Treatment with a mercaptoethanol, disulfide reducing agent, led to fragmentation of the allergens with over 90 percent becoming dialyzable. The allergens were undigestable with common proteolytic enzymes. The absorption spectrum of the aqueous extract had almost no maximum at 280 nm, the characteristic protein peak, but seemed to resemble the spectrum of S-carboxymethyl-tachis keratose. On agarose gel electrophoresis, the allergens migrated in one extended polydisperse band, again resembling solubilized keratin derivatives. It proved impossible to raise precipitating antibodies to feather allergens in rabbits. When six patients with positive skin test reactions to house dust extract were skin tested with this extract and the nondialyzable fraction (0.2 microgram per test), the feather extract appeared to be at least 10 times less potent on a weight basis than the house dust extract. Berrens concluded that, from the chemical point of view, the allergens in his extract of aged feathers were very complex and evaded characterization. He believes that the allergenicity of feather extracts cannot be explained on the basis of their content of house dust allergens. However, that possibility was not ruled out.

d. *Standardization.* There are no data on the specificity of individual feather extracts, except for those in the few studies in which they are compared to house dust extract. There is no established references standard for these extracts. No information is available on the potency or stability.

e. *Labeling.* Refer to the general statement on labeling.

f. *Safety.* No information is available on the safety of these products for use in diagnosis and therapy.

g. *Effectiveness*—(1) *For diagnosis.* No information was provided by the manufacturers demonstrating the effectiveness of feather extracts for the diagnosis of allergy to feathers of one sort or another. The Panel found no critical study of the question. Several reports cited above do provide data on the frequency of positive skin reactions to unstandardized feather extracts.

Coca et al. (Ref. 71) stated that since feather extracts used most often contained mixtures of feathers from different species of birds, it is questionable whether variations in the reported sensitivity to chicken, duck and goose feathers could be attributed solely to the difference in exposure to each. They said that it was more likely that the quality of the extracts used in testing was responsible for these variations. These extracts are usually rather weak allergenically when compared with extracts of mammalian epithelia. Even at high concentrations, they rarely induce constitutional reactions. According to Coca et al. (Ref. 71), these extracts are so unreliable that the results of studies on the specificity of different feather allergens should be disregarded. A common alergen may be present in all of them.

Tuft (Ref. 112) wrote that feather extracts, because they are used at high concentrations, are likely to give nonspecific, i.e., false-positive, reactions. Proper controls (not specified) were therefore urged.

(2) *Effectiveness for therapy.* No information was provided by the manufacturers demonstrating the effectiveness of feather extracts for the treatment of allergy to birds or feathers.

Although feather extracts have been used for immunotherapy, the Panel found only one report of treatment with feather extract, and that was with an emulsified extract. Halpin and Prince (Ref. 130), in reporting their collaborative study, concluded that it was not possible to obtain significant data since most patients were clinically sensitive to several allergens (including house dust) besides feathers. Furthermore, standardized treatment regimens were not used. More important, no details of any aspects of the study were given in the paper. Thus, this report provides no evidence for the therapeutic efficacy of feather extracts.

h. *Critique and conclusions.* Allergy to birds and their feathers may occur in individuals who raise birds and in those who have contact with feathers in bedding and other household sources. However, there are no accurate data on the frequency of such allergies. Virtually nothing is known about the composition of feather extracts. The manufacturers provided no information, and the Panel found little, on the effectiveness and safety of various feather extracts for use in diagnosis and therapy. They are probably less effective than extracts of mammalian epithelia. Avoidance of the environmental sources of these allergens is generally regarded as the most appropriate therapeutic

recommendation to patients diagnosed as being allergic to feathers.

Additional investigations are needed to ascertain the clinical value of these extracts. Especially important would be a clearer definition of these allergies from the clinical point of view, better definition of the source materials used in the preparation of various feather extracts, and characterization of the components of extracts of feathers from individual species of birds. Attention must be paid to the difference between freshly plucked feathers and aged feathers, and to the possibility of allergens common to house dust.

i. *Recommendations.* It is recommended that feather extracts be placed in Category IIIA for both skin test diagnosis and immunotherapy.

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C. Mold Allergenic Extracts

1. *Introduction.* Since the pioneer work by Storm van Leeuwen in the third decade of this century there has been increasing evidence of the importance of allergy to various inhaled specific mold spores in the etiology of asthma and hay fever (Refs. 1 through 58). A large number of molds have been identified as allergens on the basis of two criteria:

a. *Proven exposure.* Large amounts of the specific mold spore have been demonstrated repeatedly in air breathed by the patient with asthma and/or hay fever.

b. *Positive skin test.* Extracts of the particular mold spore produce a positive immediate cutaneous or intradermal reaction in the same patient with asthma and/or hay fever.

Extracts of all or most of the mold spores meeting these criteria have been licensed for use for diagnostic skin testing and immunotherapy (Table 1). However, only a fraction of these have proven to be allergenic on the basis of the two criteria listed above to qualify for Category I for diagnosis plus the following third and fourth essential criteria if a product is to be placed in Category I for immunotherapy:

c. *Clinical correlation.* The patient with symptoms who is known to have environmental exposure and positive skin and/or laboratory tests must also be shown to improve symptomatically and immunologically with immunotherapy.

d. *Safety.* Safety must also be established.

2. *Manufacturing.* Stock cultures of molds are obtained as isolates from air and soil-samples or from culture collections such as the American Type Culture Collection. Two general methods have been used for obtaining allergenic extracts from the mature growth cultures.

a. *Regular process.* At the end of the incubation period (usually two to three weeks), the mature growth in the production cultures is separated from the medium and dried. The dried mole is ground to a powder and stored in sealed containers at 20 to 24 degrees C until ready for use for preparing extract. The dried mold material is extracted with extracting fluid, sterilized by filtration, and thereafter processed like other allergenic extracts.

b. *MMP process.* This type of mold extract has been prepared under franchise from the Association of Allergists for Mycological Investigation. The graduate mycologist for this organization maintains the stock cultures and provides them to the manufacturer.

The production medium is chemically defined and consists of low molecular weight dialyzable compounds. At the end of the 5-week incubation period, the growth and broth are separated and the broth is concentrated, dialyzed, and dehydrated by freeze-drying. This dry material contains the nondialyzable mold metabolites including the allergens. It is stored in sealed containers at 1 to 5 °C until ready for use in preparing liquid extract.

Liquid extract is prepared by reconstitution of the dry material in either 50 percent glycerin and 0.9 percent NaC1 solution, or a buffered saline preservation solution. The extract is sterilized by filtration. The stock

concentrate is tested for sterility and general safety. The extract is stored at 1 to 5 °C.

c. *Manufacturing recommendations.* (1) A record should be maintained of the source, history, and identifying characteristics of each stock culture. Stock cultures should be aseptically inoculated on sterile growth medium and incubated.

(2) Production seed cultures should be prepared from stock cultures by mycologists or specially trained graduate microbiologists who are qualified to verify purity and identity prior to inoculation, and during growth of the production broth cultures.

(3) Dried mold source material prepared by either process should be kept no longer than 5 years unless data indicate that a different storage time is appropriate.

(4) Also, see the Mycotoxin section of the earlier discussion under "Safety."

3. *Safety.* The principles of safety of mold extracts are covered in the general sections on safety of allergenic extracts and on mycotoxins. Two additional problems are noted with mold extracts:

a. Local and asthmatic reactions occur frequently when injections of *Aspergillus fumigatus* extract are employed for immunotherapy of allergic bronchopulmonary aspergillosis and, therefore, such immunotherapy is not recommended (Refs. 32 and 36). These reactions have been attributed to antigen antibody complexes formed by combination of injected antigen with precipitating IgG antibodies to *Aspergillus fumigatus* which are present in this syndrome (Refs. 32 and 36). They may also in part be related to the high levels of specific IgE antibody which have been demonstrated in some of these patients (Ref. 59).

b. Late reactions to immunotherapy with *Alternaria* allergenic extracts occur in some patients and consist of fever, malaise, and painfull swelling at the site of injection. Such a late reaction developed in one of 23 patients who were followed prospectively during the first year of immunotherapy with *Alternaria* extract (Ref. 47). These late reactions to *Alternaria* extract may also occur when the *Alternaria* extract is one component of an allergenic extract mixture. In seven patients who had experienced a late reaction to injection of an immunotherapy mixture, elimination of the *Alternaria* extract from the immunotherapy mixture resulted in disappearance of the late reaction (Ref. 47). These late reactions are sufficient cause for discontinuing immunotherapy with *Alternaria* extract (Ref. 47). These late reactions have been noted to occur in patients with IgG and IgE serum antibodies to *Alternaria*. However, both IgG and IgE antibodies to *Alternaria* may be found in the absence of these reactions and, therefore, neither is sufficient cause for discontinuing *Alternaria* immunotherapy in the absence of late reactions.

4. *Effectiveness*—a. *Effectiveness of mold extracts for skin test diagnosis.* The Panel found evidence that a properly performed and interpreted skin test with some specific mold extracts may be of value as an aid in the diagnosis of hay fever and/or asthma induced by inhalation of the specific mold spore. The Panel considered the following in evaluating these studies:

(1) *Verification of diagnosis.* The following are difficulties in establishing the diagnosis of hay fever and/or asthma from inhalation of specific mold spores:

(i) *Variable exposure.* Outdoors, molds may typically grow on various forms of vegetation, such as grain, and spores may be in the air from the beginning of the growing season until the ground is covered by snow (Refs. 3, 8, 9, and 25). Inside buildings, molds may grow under suitable conditions at any time of the year (Refs. 1, 4, 10, 21, and 44). The presence of spores in either indoor or outdoor air can be quantitated easily by doing spore counts on greased slides exposed by the same method used for pollen counts or by exposing culture plates (Refs. 3, 9, 10, 15, 25, and 30). The duration of outdoor exposure, therefore, depends on the length of the season between the end and the start of snow and will be shorter in the North than farther South, and year-around in some areas where there is no snow. The amount of exposure will vary with the availability of favorable growth conditions for the mold which include proper substrates, temperatures, and water contents.

(ii) *Multiple inhalant allergen exposure.* Specific mold exposure occurs at times when patients are also exposed to other major inhalant allergens including other molds, house dust, and various pollens (Refs. 2 through 6, 8 through 10, 14, 15, 29, 30, and 42 through 45). The Panel sought studies which showed whether or not the observed symptoms were due to the specific mold or to other allergens. Reports were found:

(*a*) Studying patients who were sensitive only or mainly to a single mold (Refs. 1, 3, 21 through 23, 26, and 27).

(*b*) Studying patients in specific geographical areas who have seasonal symptoms when a single mold is the major allergen (Refs. 3, 14, 25, 29, and 49). Other seasonal outdoor molds can confuse such studies and are difficult to exclude because of cross-antigenicity, such as between the *Dematiaceae* molds (Refs. 11 and 12).

(*c*) Studying patients with asthma and/or hay fever after exposure to an environment known to contain the specific spore (Refs. 1, 2, 14, 21, 22, 23, 26, and 27).

(*d*) Studying patients with typical eye, nose, or bronchial symptoms and signs after appropriate provocation tests in which powdered or liquid extracts were applied to the eyes, nose and/or bronchi (Refs. 1, 4 through 6, 8, 14, 15, 27, 28, 42, 45, and 52).

(2) *Extract potency for skin test diagnosis.* Studies were found demonstrating that potent extracts could be obtained by the regular process (Refs. 1, 4 through 6, 8, 14, 15, 21, 23, 26, 27, 42, and 45) and the MMP process (Refs. 6 and 7).

(3) *Irritative versus specific reactions.* The Panel sought evidence that the diagnostic wheal and flare reactions were induced by the specific antigen and not by some other irritative substance in the extract, diluent, syringe or needle. The Panel noted whether appropriate controlled skin tests were performed with the extract on nonallergic patients and on the tested patients with diluent, syringe and needle controls. The Panel would like to have evidence that the injection techniques were sufficiently gentle to avoid the normal triple response to skin injury (Ref. 13) and that dermatographism and universal reactors were ruled out.

(4) *Variable skin test reactivity.* Clinically sensitive patients who have asthma and hay fever after inhaling specific mold spores usually have positive skin tests to the mold extracts, but do not have equal skin reactivity. Most will react to low doses of the mold extract, a few will react to high doses only (Refs. 1 through 8, 14, 15, 21, 22, 23, 26, 27, 28, 32, and 45).

Many atopic patients who are clinically free of symptoms after exposure to the specific spores but who have asthma and/or hay fever symptoms induced by exposure to other allergens (henceforth called clinically insensitive patients) will have a positive skin reaction to the specific mold extract (Refs. 2, 4, 5, 6, 8, 14, 15, 24, 45, and 52). This type of clinically insensitive patient commonly is "less skin reactive" than the clinically sensitive patient, in that higher doses on the average are needed to elicit the reaction. Nevertheless, there are some clinically insensitive patients who react to low doses of the extract and some clinically sensitive patients who react to high doses. Therefore, a positive skin reaction to a certain

concentration of the specific mold extract alone is not diagnostic of clinical allergy to that mold and should not be the sole diagnostic basis for initiating immunotherapy.

(5) *Mold extract value in diagnosis.* The presence of both skin reactions to low doses of the specific mold extract and hay fever and/or asthma after inhalation of the mold spore is usually diagnostic of specific mold-induced hay fever and/or asthma. Both phenomena are required to have reasonable certainty of the diagnosis. The more typical the symptoms of asthma and hay fever, the more clear the relation of these symptoms to inhalation of the specific mold spores, the smaller the amount of specific mold antigen needed to elicit skin reactivity, and the smaller the number of factors other than the specific mold spore which produce hay fever and/or asthma, the greater the reliability of the diagnosis that allergy to the specific mold is at least one cause of the patient's hay fever and/or asthma.

b. *Effectiveness of mold extracts for immunotherapy*—(1) *Clinical trials.* Controlled clinicial trials have been discouraged by the difficulty in establishing a definite diagnosis as discussed previously, the difficulty in demonstrating the presence or absence of exposure to the specific spores as discussed previously, and the absence of a reference standard of potency such as antigen E affords for ragweed pollen extract.

Therefore, the Panel found that there is no conclusive proof by adequate and well-controlled clinical trials of the effectiveness of the specific mold spore extracts for immunotherapy. In view of the clinical impression from uncontrolled studies that this immunotherapy is effective and the general assumption that properly given immunotherapy with any specific allergen will reduce the severity of symptoms of asthma and/or hay fever due to the inhalation of that particular allergen, it would seem highly likely that suitable controlled studies would demonstrate the effectiveness of mold extract immunotherapy. Such conclusive studies probably will require development of suitable methods for:

(i) Testing by mucosal provocation for conclusive diagnosis of the mold sensitivity.

(ii) Delivering exposure to the specific spore under controlled conditions. Fontana's "controlled environment" might be adapted for this purpose (Ref. 20). Harris (Ref. 2) used such a method.

(iii) Quantitating severity of symptoms induced by natural exposure to specific spores. The symptoms diaries used in the studies of immunotherapy of ragweed pollenosis could be used for this purpose.

(iv) Standardizing mold extracts to assure that sufficient antigen is given (Ref. 49).

(2) *Immunologic evidence.* The Panel also sought immunologic evidence of effectiveness including:

(i) An increase in specific mold spore IgG blocking antibody,

(ii) A decrease in the expected rise in mold spore specific IgE antibody during the mold season,

(iii) Progressive decrease in mold spore specific IgE antibody during the course of many years of immunotherapy with the specific mold spore extract,

(iv) Progressive decrease in skin reactivity to the extract during the course of many years of immunotherapy with the extract, and

(v) Decrease in leukocyte histamine release by the specific mold spore extract after immunotherapy with the extract.

Obviously, older studies did not contain detailed immunologic evidence because the technology did not exist.

5. *Potency.* There is no chemical standard of potency for any of the mode extracts such as Antigen E provides for short ragweed pollen extract.

Yunginger, Roberts, and Gleich (Refs. 46 and 49) studied the potency of commercial *Alternaria* extracts by endpoint skin test titrations and by chromatographic and radioallergosorbent test procedures and showed that extracts from different companies were neither qualitatively nor quantitively comparable. Neither weight-to-volume designation nor the PNU content bore any relationship to allergenic potency as measured by skin testing or radioallergosorbent test procedures. Extracts differed by as much as 3,000-fold in allergen content by skin testing. Moreover, the extracts appeared to contain different allergenic determinents when tested by the radioallergosorbent test procedures.

6. *Antigenic specificity*—a. *Dematiaceae.* There is considerable evidence of both cross-reacting and distinct antigens in various genera and species of the *Dematiaceae*, particularly *Alternaria, Helminthosporium, Curvularia, Spondylocladium, Stemphylium Hormodendrum* and *Pullularia.* This has been demonstrated by skin testing (Ref. 12), neutralization of passive transfer (Ref. 57), antigen binding (Refs. 51 and 56) and gel diffusion (Ref. 11) techniques. The genera specific antigens may be the only important ones in a particular case and therefore all should be available for diagnostic studies and immunotheraphy (Ref. 12). There are reports of patients sensitive to only one species of dematiaceous mold; for example, a patient who reacted to *Cladosporium fulvum*, but not to *Cladosporium herbarum* or to *Alternaria* or *Pullularia* (Ref. 58).

Schumacher and Jeffrey (Ref. 50) have presented evidence which indicates that both the strain of *Alternaria tenuis* (syn. *A. alternate*) and the conditions of culture might influence the specificity of the extract. Well defined, potent, mold cultures will demand careful attention to both mold strain and cultural conditions.

b. *Aspergilli.* There is evidence of cross-reacting and distinct antigens among the *Aspergilli.* Pennington (Ref. 15) demonstrated different patterns of skin reaction to *Aspergillus fumigatus, Aspergillus niger, Aspergillus ochrochus, Aspergillus flavus,* and *Aspergillus glaucus,* and to different extracts of *Aspergilli* of the same species in patients known to be sensitive to *Aspergilli.* McCarthy and Pepys (Ref. 32), demonstrated different patterns of skin reaction to *Aspergillus fumigatus* and *Aspergillus terreus* in patients with allergic bronchopulmonary aspergillosis. Weiner (Ref. 41) and Argabrite, Morrow and Meyer (Ref. 33) showed different patterns of skin reaction to extracts of *Aspergillus flavus, Aspergillus fumigatus, Aspergillus nidulans, Aspergillus glaucus, Aspergillus niger, Aspergillus sydowi,* and *Aspergillus terreus.* Slavin, Stanczyk, Lonigro, and Broun (Ref. 39) reported skin reactions of differing intensity to *Aspergillus fumigatus, Aspergillus niger, Aspergillus horteli,* and *Aspergillus flavus* extracts in a patient with allergic bronchopulmonary aspergillosis. Goldstein and Yokayama (Ref. 34) using passive transfer neutralization techniques, demonstrated common and unique antigens in extracts of *Aspergillus fumigatus, Aspergillus terreus, Aspergillus niger,* and *Aspergillus glaucus.* They further showed that *Aspergillus fumigatus* precipitins in the serum of a patient with allergic bronchopulmonary aspergillosis could be adsorbed by *Aspergillus fumigatus* extract, but not by *Aspergillus terreus, Aspergillus niger* and *Aspergillus glaucus* extracts.

Because of these species specific antigens, the allergist needs extracts of multiple species of *Aspergilli.* Experience with variation in aflatoxin production by various strains of *Aspergillus flavus,* and by the same strain under different conditions of culture (see statement on Mycotoxins), suggests that the assurance of well-defined, potent mold extracts will demand intensive study of the effects of

strain and cultural conditions on specificity.

7. *Recommendations for mold extracts for use in inhalant allergy* a. Six specific mold spore extracts have been shown to be effective aids for the diagnosis of hay fever and/or asthma induced by inhaling specific molds spores. These are *Alternaria, Cladosporium (Hormodendrum), Helminthosporium, Aspergillus, Penicillium* and *Mucor.* Therefore, the Panel recommended that they be placed in Category I for skin test diagnosis.

There is less definite but suggestive evidence indicating that five other extracts reviewed in detail by the Panel may also be effective for skin test diagnosis. These are *Botrytis, Candida albicans, Cephalothecium roseum, Monilia stiophial* and *Pullularia.* The Panel recommended that these be placed in Category IIIA for skin test diagnosis.

The evidence of effectiveness for skin test diagnosis for each of the above 11 extracts is reviewed in detail in the sections which follow.

b. The 11 extracts listed above have also been used for immunotherapy of patients with asthma and/or hay fever due to the specific mold spores. There are no controlled studies indicating the effectiveness of any of these extracts for reducing the severity of symptoms of hay fever and asthma. Therefore, there is no conclusive proof of the effectiveness of immunotherapy with these extracts. In view of the clinical impression from uncontrolled observations that this immunotherapy is effective, and the general assumption that properly given immunotherapy with any specific allergen will reduce the severity of symptoms of hay fever and/or asthma due to inhaling that particular allergen, it would seem likely that suitable controlled studies would demonstrate the effectiveness of immunotherapy with these extracts. The Panel recommends, therefore, that all 11 of these extracts be placed in Category IIIA for immunotherapy. The reported evidence of effectiveness of immunotherapy with these 11 specific mold spore extracts and associated immunologic reactions is reviewed in the sections which follow.

c. It would seem likely that other specific mold spore extracts have been or will be found to be effective. Based upon the expected antigenic composition of the other mold extracts in comparison with the studies reported below, the Panel recommends that all other mold extracts in Table I and any others licensed as allergenic extracts not specifically reviewed be placed in Category IIIA for both skin test diagnosis and immunotherapy of hay fever and/or asthma induced by exposure to the specific mold spores.

d. The Panel recommends that work similar to that of Yunginger et al. (Refs. 46 and 49) be encouraged on each specific mold allergenic extract so that standard extracts of well-defined allergen content can be developed which can serve as reference standards for assuring the potency of commercial mold allergenic extracts.

TABLE 1.—SPECIFIED MOLD SPORE EXTRACTS

Asidia capillata	*Beauveria bassiana.*
Achorion schoenleini	*Bispora antennata.*
Acrothecium spp	*Botrytis.*
Alternaria	*Botrytis cinerea.*
Alternaria solani	*Candida albicans.*
Alternaria tenuis	*Candida (Monilia) albicans.*
Anacystis	*Candida krusei.*
Aspergillus spp.	*Candida stellatoidea.*
Aspergillus amsterdami	*Candida tropicalis.*
Aspergillus clavatus	*Cephalosporium.*
Aspergillus flavus	*Cephalosporium acremonium.*
Aspergillus flavus oryzae	*Cephalothecium.*
Aspergillus fumigatus	*Cephalothecium (Trichothecium) roseum.*
Aspergillus glaucus	*Chaetomium.*
Aspergillus nidulans	*Chaetomium globosum.*
Aspergillus niger	*Chaetomium indicum.*
Aspergillus restrictus	*Chaetomium olivaceum.*
Aspergillus sydowi	*Chlamydomyces diffusus.*
Aspergillus terreus	*Chlorella.*
Aspergillus ustus	*Cladosporium.*
Aspergillus versicolor	*Cladosporium cladosporiodes.*
Aspergillus wentii	*Cladosporium fulvum.* *Cladosporium herbarum.*
Cladosporium resinae	*Fomes sp.*
Cladosporium sphaerospermum.	*Fusarium moniliforme.*
Cladosporium werneckii	*Fusarium oxysporium.*
Colletotrichum	*Fusarium roseum.*
Cryptococcus sp.	*Fusarium solani.*
Cryptococcus diffluens	*Fusarium vasinfectum.*
Cryptococcus laurentii	*Geotrichum.*
Cryptococcus terreus	*Geotrichum (Oospora).*
Cunninghamella elegans	*Geotrichum oidium.*
Curvularia	*Gliocladium.*
Curvularia geniculata	*Gliocladium derquescens.*
Curvularia inaegualis	*Gliocladium fimbriatum.*
Curvularia lunata	*Gliocladium roseum.*
Curvularia spicifera	*Helminthosporium.*
Dematium nigrum	*Helminthosporium interseminatum.*
Epicoccum	*Helminthosporium maydis.*
Epicoccum cinnabarium	*Helminthosporium sativum.*
Epicoccum nigrum	*Helminthosporium solani.*
Epicoccum purpurascens	*Hormodendrum (see Cladosporium).*
Epidermophyton	*Hormodendrum hordei.*
Epidermophyton floccosum (inguinale).	*Lycopodium.*
Epidermophyton rubrum	*Microsporum.*
Microsporum audouinii	*Mycogone nigra.*
Microsporum canis (lanosum)	*Mycogone nigra nigrospora.*
Microsporum gypseum	*Mycogone rosea*
Monilia	*Mycotypha dichotoma.*
Monilia albicans	*Neurospora crassa.*
Monilia apiospermum	*Nigrospora sp.*
Monilia crassa	*Nigrospora oryzae.*
Monilia sitophilia	*Nigrospora sphaerica.*
Monilia sitophilia neurospora	*Oidiodendrum sp.*
Monilia (candida) tripicalis	*Oidiodendrum oospara.*
Monotospora lanuginosa	*Paecilomyces.*
Mucor	*Paecilomyces elegans.*
Mucor circinelloides	*Paecilomyces variota.*
Mucor lamprospora	*Paecilomyces (spicaria) varitota.*
Mucor mucedo	*Papularia arundinis.*
Mucor plumbeus	*Penicillium.*
Mucor racemosus	*Penicillium atramentosum.*
Mucor rhizopodoformis	*Penicillium biforme.*
Mucor rouxii	*Penicillium camemberti.*
Mushroom	*Penicillium carmino-violaceum.*
Mycelia sterilia	*Penicillium chrysogenum.*
Mycogone sp.	*Penicillium digitatum.*
Penicillium elaucum	*Rhizopus.*
Penicillium expansum	*Rhizopus arrhizus.*
Penicillium glaucus	*Rhizopus nigricans.*
Penicillium intricatum	*Rhodotorula.*
Penicillium italicum	*Rhodotorula glutinis.*
Penicillium luteum	*Rhodotorula rubra.*
Penicillium megasporum	*Saccharomyces sp.*
Penicillium notatum	*Saccharomyces cerevisiae.*
Penicillium roqueforti	*Scopulariopsis.*
Penicillium roseum	*Scopulariopsis brevicaulis.*
Penicillium rubrum	*Spondylocladium.*
Phoma	*Spondylocladium atrovirens.*
Phoma batae	*Sporobolomyces.*
Phoma destructiva	*Sporobolomyces salmonicolor.*
Phoma herbarum	*Sporotrichum.*
Phycomycetes	*Sporotrichum pruinosum.*
Phycomyces blakesleeanus	*Stachybotrys atra.*
Pleospora sp.	*Stemphylium (macrosporium).*
Podaxis sp.	*Stemphylium botryosum.*
Poria sp.	*Stemphylium lanuginosum.*
ullularia	*Stemphylium sakciniforme.*
Pullularia pullulans	*Stemphylium solani.*
Penicillium luteum	*Penicillium megasporum.*
Penicillium notatum	*Penicillium roqueforti.*
Treptomyces	*Trichophyton gypseum.*
Streptomyces griscus	*Trichophyton interdigitale.*
Syncephalastrum racemosum	*Trichophyton mentagrophytes.*
Tetracoccosporium	*Trichophyton purpureum.*
Thamnidium elegans	*Trichophyton rubrum.*
Torula (Rhodotorula)	*Trichophyton (achorion) schoenleinii.*
Tirchoderma sp.	*Trichophyton tonsurans.*
Trichoderma lignorum	*Trichophyton yioleceum.*
Trichoderma viride	*Trichothecium.*
Trichophyton	*Trichothecium roseum.*
Trichophyton cutaneum	*Typhula.* *Verticillium albo-atrum.*

Reviews of Specific Mold Extracts

1. *Alternaria*—a. *Effectiveness of Alternaria Extract for skin test diagnosis.* The reported evidence indicates that a properly performed and interpreted skin test may be of considerable value as an aid in the diagnosis of hay fever and/or asthma induced by inhalation of *Alternaria* spores (Refs. 1 through 8, 14, 15, 48, 49, and 52).

Hopkins, Benham and Kesten (Ref. 1) studied one patient who had asthma when in a cellar where *Alternaria* spores were abundant in the ambient air and also after inhalation of cultured *Alternaria* spores. Direct skin tests, passive transfer skin tests, and bronchial challenge tests with *Alternaria* extract were positive. The extracts were made by the authors by taking the pellicle (a film on the surface of a liquid) from old *Alternaria* cultures, washing it, grinding it with carbon dioxide snow and sand, and extracting the mold powder with a phenol saline solution.

Harris (Ref. 2) studied 12 patients who had increase in symptoms of hay fever and/or asthma in the *Alternaria* season. All had positive reactions to skin tests with *Alternaria* extracts. Ten of 12 exposed had symptoms of hay fever

and/or asthma when placed in room air containing *Alternaria* spores. Ten patients who did not have an increase in symptoms of hay fever or asthma in the *Alternaria* season but who had positive reactions to skin tests with *Alternaria* extract were also placed in room air containing *Alternaria* spores and only one of these developed asthma in this environment.

Feinberg (Ref. 3) studied 50 patients who had symptoms of hay fever and/or asthma in the *Alternaria* season. All had positive skin tests to *Alternaria* extracts. Passive transfer tests were positive in "most of the instances in which it was tried," though the number of patients tested in this manner was not stated. Control tests done on the normal recipients of the passive transfer tests were negative except in the site sensitized.

Chobot, Dundy and Schaffer (Ref. 4) studied 12 patients who had hay fever and/or asthma and who had a positive reaction (nasal swelling and sneezing) when *Alternaria* spores were applied to the nasal turbinates. All had positive reactions to direct skin, passive transfer skin, and ophthalmic tests with *Alternaria* extracts. Sixteen additional patients with hay fever or asthma had positive reactions to skin tests but negative reactions to ophthalmic tests with *Alternaria* extract. Six of the 16 had positive passive transfer tests. None of the 16 had a positive reaction when *Alternaria* spores were placed in the nose. The mold extracts were made in the laboratories of the New York Post-Graduate Hospital. A thick pellicle of *Alternaria* was grown in dextrose broth, washed with saline, killed with 95 percent alcohol, dried in a dessicator and ground up. The mold powder was extracted with buffered saline.

Blumstein (Ref. 5) studied 10 patients who had hay fever and/or asthma in the *Alternaria* season and positive nasal reaction to dried powdered *Alternaria* pellicle. All had positive direct skin tests; passive transfer skin tests were positive in at least 8 of the 10. Thirty-one additional patients with positive skin tests to *Alternaria* extracts had negative nasal challenge tests with dried powdered *Alternaria* pellicle. Skin tests with *Alternaria* extracts were negative in 365 patients. The *Alternaria* extracts were made by the author. The mold was grown for 3 weeks in liquid peptone meat extract media. The pellicle was removed, killed in a sterilizing jar over 40 percent formalin, air dried, ground to a fine powder, and extracted with Coca's solution.

Halpern, Holman, and Whittaker (Ref. 6) studied 38 patients with hay fever and/or asthma who had positive responses to nasal provocation tests with *Alternaria* MMP extracts. All had positive reactions to skin tests with *Alternaria* MMP extracts. Twenty-two additional patients with hay fever and/or asthma had positive reactions to skin tests with *Alternaria* MMP extract, but negative reactions to nasal provocation tests with *Alternaria* MMP extract. Furthermore, all of 26 patients with hay fever and/or asthma who had positive reactions to nasal provocation tests with *Alternaria* type 33 extracts had positive reactions to skin tests with *Alternaria* type 33 extracts (Ref. 7). However, an additional 21 patients with positive reactions to skin tests with *Alternaria* type 33 extracts had negative reactions to provocation tests with these extracts. Finally, all of 23 patients with hay fever and/or asthma who had positive reactions to nasal provocation tests with standard *Alternaria* extracts had positive reactions to skin tests with standard *Alternaria* extracts. However, an additional 31 patients with positive reactions to skin tests with standard *Alternaria* extracts had negative reactions to nasal provocation tests to these extracts. No skin tests in normal control patients were reported. *Alternaria* MMP extract was obtained from the Association of Allergists for Mycological Investigation. *Alternaria* type 33 extract was obtained from Hollister-Stier (Ref. 7). Standard *Alternaria* extract was prepared by the author by extracting dried powder of *Alternaria* from "three reliable commercial sources" in Hollister-Stier's solutions.

Prince (Ref. 7) studied 55 patients who had been determined to be sensitive to *Alternaria* before the onset of the study, mainly by demonstrating positive reactions to skin tests with other *Alternaria* extracts. All of these patients had a positive skin test to *Alternaria* MMP extract (88 percent reacted to cutaneous tests with 1:50 dilution and 100 percent reacted to intradermal tests with 1:1000 dilution). On the other hand, 69 patients who had been determined insensitive to *Alternaria* before the onset of the study, mainly by demonstrating negative reactions to skin tests with other *Alternaria* extracts, usually had negative skin reactions to *Alternaria* MMP extracts (two percent reacted to cutaneous tests with 1:50 dilution and 18 percent to intradermal tests with 1:1000 dilution). Extracts were obtained from Hollister-Stier.

Ripe (Ref. 8) studied 30 patients with symptoms of rhinitis and/or asthma who has positive skin tests to *Alternaria* extract. Nasal or bronchial provocation tests were positive in 10 of the 30, and in 9 of 12 of those whose skin reacted to low concentrations of the extract. In addition, they studied two patients with hay fever or asthma who had negative skin tests with high concentrations of *Alternaria* extract. Both had negative provocation tests. Extracts were made by the author. The mold was cultured in liquid media, harvested, disintegrated, and extracted with 0.1 M sodium phosphate containing 0.015 M sodium citrate.

Pennington (Ref. 14 and 15) studied four patients with hay fever and/or asthma who had asthma or hay fever when *Alternaria* mold spores were applied to the membranes of their nose and throat. All four had positive reactions to direct skin tests and passive transfer tests with *Alternaria* extracts. Four normal control patients had no symptoms of hay fever or asthma when mold spores were applied to the membranes of their nose and throat and negative skin tests to *Alternaria* extracts.

Hoffman and Haddad (Ref. 48) studied 69 patients who were felt to have a positive history of *Alternaria* allergy and/or a positive reaction to skin test with *Alternaria* extract. Sixty of these had a positive radioallergosorbent test to *Alternaria*. Patients with strongly positive radioallergosorbent tests usually but not invariably, had positive skin tests and patients with strongly positive skin tests usually but not invariably, had positive radioallergosorbent tests. *Alternaria* extracts were supplied by Hollister-Stier or Allermed Laboratories.

Yunginger, Jones and Gleich (Ref. 49) studied the end point skin test potency of 12 different commercial *Alternaria* extracts in 10 patients with clinical histories suggesting *Alternaria* sensitivity. *Alternaria* extracts produced positive skin reactions in all, and the end point potency of each extract correlated with the potency determined by both radioallergosorbent test inhibition and direct radioallergosorbent test assays. The extracts of *Alternaria* were purchased from 12 different United States companies.

Bronsky and Ellis (Ref. 52) studied the reactions of 32 children to cutaneous and intracutaneous skin tests and bronchial challenge tests with a mixture of mold extracts containing *Alternaria, Hormodendrum, Penicillium,* and *Aspergillus.* Forty-two challenges were done on 31 patients. When the cutaneous test was positive, 77 percent of the bronchial challenges were positive. Where the intradermal test was positive, but the cutaneous test was negative, only 26 percent of the bronchial challenges were positive. All

10 challenges done in the presence of completely negative skin tests were negative. Mold extracts were obtained from Center, Hollister-Stier, or Endo Laboratories.

b. *Effectiveness of Alternaria Extract for Immunotherapy.* Tuchinda and Chai (Ref. 19) have studied the effects of immunotherapy with *Alternaria* extract in children with chronic asthma. They diagnosed *Alternaria* asthma on the basis of (1) positive skin test to *Alternaria* extracts, (2) positive inhalation test to *Alternaria* extract, and (3) a history in keeping with asthma induced by inhalation of *Alternaria* spores. They showed that bronchial sensitivity to *Alternaria* extract was decreased after "high dose" immunotherapy with a cumulative dose of 31,665 to 121,025 PNU give over a period of 5 to 12 months, but was not significantly decreased after "low dose" immunotherapy with a cumulative dose of 1,327 to 8,307 PNU given over a period of 3 months (Table 2).

TABLE 2.—EFFECTS OF HIGH AND LOW DOSE IMMUNOTHERAPY WITH "ALTERNARIA" EXTRACT (REF. 19)

Patient	Cumulative dose in PNU	Duration of immunotherapy in months	Bronchial sensitivity [1]	
			Pretreatment dose in PNU	Posttreatment dose in PNU
A. High dose group:				
1	31,665	5	700	8,200
2	40,051	7	1,450	8,000
3	121,025	12	700	4,000
4	48,681	7	1,500	5,000
5	47,177	8	1,700	3,250
6	119,714	9	120	3,000
B. Low dose group:				
1	1,327	3	120	140
2	8,307	3	700	1,200

[1] Bronchial Sensitivity—The inhaled does of *Alternaria* extract required to induce either 25 percent decrease in peak expiratory flow rate or frank asthma.

Schumacher and May (Ref. 16) and May, Lyman, Alberto and Aduna (Ref. 17) have studied immunologic reactions to immunotherapy with *Alternaria* extracts. Increase in blocking antibody (serum antigen neutralizing capacity) was demonstrated in all patients studied. This increase was very marked in some patients receiving high doses. This blocking antibody is presumably IgG antibody, but definitive studies to prove this point were not done. Skin reactivity and leukocyte sensitivity to *Alternaria* antigen were not significantly reduced in most instances, though patients received up to 2 years of immunotherapy with what are generally considered to be adquate of this extract. Some patients had an increase in leukocyte sensitivity during the first 4 weeks of intensive immunotherapy. One patient receiving very high doses of *Alternaria* extract experienced complete loss of leukocyte sensitivity to *Alternaria* and unrelated antigens for a brief period (Ref. 18).

There were no studies found about other immunologic reactions after immunotherapy with *Alternaria* extract.

There are no controlled studies indicating the effectiveness of *Alternaria* extract for reducing the severity of symptoms of hay fever and/or asthma induced by inhalation of *Alternaria* spores. Therefore, there is no conclusive proof of the effectiveness of *Alternaria* extract immunotherapy. In view of the clinical impression from other uncontrolled studies that this immunotherapy is effective (Refs. 3, 5, and 14) and the general assumption that properly given immunotherapy with any specific allergen will reduce the severity of symptoms of asthma and/or hay fever due to the inhalation of that particular allergen, it would seem highly likely that suitable controlled studies would demonstrate the effectiveness of *Alternaria* extract immunotherapy.

c. *Recommendations for Alternaria extract.* (1) *Alternaria* extract is an effective aid for the diagnosis of hay fever and/or asthma induced by the inhalation of *Alternaria* spores. In a patient with typical manifestations of hay fever and/or asthma after the inhalation of *Alternaria* spores, a correctly interpreted positive skin reaction to a properly applied low dose of *Alternaria* extract indicates that allergy to *Alternaria* is at least one cause of the hay fever and/or asthma symptoms.

(2) Uncontrolled studies suggest that properly administered immunotherapy with *Alternaria* extract may be an effective method for reducing the severity of symptoms of hay fever and/or asthma induced by inhalation of *Alternaria* spores.

Alternaria extract immunotherapy is associated with an increase in anti-Alternaria blocking antibodies.

(3) The Panel recommends that *Alternaria* extracts be placed in Category I for skin test diagnosis, and in Category IIIA for immunotherapy.

2. *Cladosporium*—a. *Effectiveness of Cladosporium Extract for skin test diagnosis.* The reported evidence indicates that a properly performed and interpreted skin test may be of considerable value as a diagnostic aid in the diagnosis of hay fever and/or asthma induced by inhalation of *Cladosporium* spores (Refs. 5 through 8, 14, 15, 21 through 24 and 52).

Rackemann, Randolph, and Guba (Ref. 21) studied four patients who had hay fever and asthma when exposed to *Clasosporium fulvum* mold growing on tomato plants in green houses. Direct skin and passive transfer tests with *Cladosporium fulvum* extracts were positive in all four. Extracts were made by the authors. *Cladosporium fulvum* was grown on potato dextrose agar in 250-milliliter (mL) Ehrlenmeyer flasks. After maximum sporulation occurred, the growth was first moistened with 5 mL of ether and then allowed to extract in Coca's solution.

Cobe (Ref. 23) studied one patient who had hay fever and asthma when exposed to *Cladosporium fulvum* mold growing on tomato plants in a green house. Direct skin tests with *Cladosporium fulvum* extracts were positive. No skin tests in normal control patients were reported. Extracts of the mold were made by the authors. *Cladosporium fulvum* was inoculated into maltose broth and allowed to grow until a felt-like mat had covered the entire surface of the broth. The mat was powdered and extracted with 12-percent alcoholic normal saline solution.

Blumstein (Ref. 5) studied five patients who had hay fever and/or asthma in the *Cladosporium* season and positive nasal reaction to dried powdered *Cladosporium* (species not stated) pellicle. All had positive reactions to direct skin tests; at least there of the five had positive reactions to passive transfer tests. Twenty additional patients with positive skin tests to *Cladosporium* extracts has negative nasal challenge tests with dried, powdered *Cladosporium* pellicle. Three hundred eighty-one patients had negative skin reactions to the *Cladosporium* extract. The *Cladosporium* extracts were made by the author. The mold was grown for 3 weeks in liquid peptone meat extract media. The pellicle was removed, killed in a sterilizing jar over 40 percent

formalin, air dried, powdered, and extracted with Coca's solution.

Halpern, Holman, and Whittaker (Ref. 6) studied five patients with hay fever and/or asthma who had positive responses to nasal provocation test with *Cladorsporium* (species not stated) extracts. All had positive reactions to skin tests with these extracts. Fifteen additional patients with hay fever and/or asthma had positive reactions to skin tests with *Cladorsporium* extracts but negative or equivocal reactions to nasal provocation tests with *Cladorsporium* extracts. No skin tests in normal control patients were reported. Extracts were either Type 33 extracts obtained from Hollister-Stier (Ref. 7) or standard extracts made by the authors by extracting dried power of *Cladorsporium* obtained from "reliable commerical sources" in Hollister-Stier's solution.

Prince (Ref. 7) studies 46 patients who had been determined to be sensitive to *Cladosporium* before the onset of the study mainly by demonstrating positive reactions to skin tests with other *Cladosporium* extracts. Ninety-four percent of these patients had positive reactions to skin tests with *Cladosporium* (Hormodendrum Cladosporioides) MMP extracts. Forty percent reacted to cutaneous tests with a 1:50 dilution and 94 percent reacted to intradermal tests with 1:1000 dilution or less. On the other hand, 60 patients who had been determined to be insensitive to *Cladosporium* before the onset of the study mainly by demonstrating negative reactions to skin tests with other *Cladosporium* extracts usually had negative reactions to skin tests with *Cladosporium* MMP extract (Two percent reacted to cutaneous tests with 1:50 dilution, and 20 percent to intradermal tests with 1:1000 dilution or less.) Extracts were obtained from Hollister-Stier.

Ripe (Ref. 8) studied 26 patients with asthma and/or rhinitis who had positive reactions to skin tests with *Cladosporium herbarum* extracts. Nasal or bronchial provocation tests were positive in 15 of the 26, and in 13 of 15 of those whose skin reacted to low concentrations of the extract. In addition, they studied 16 patients with hay fever or asthma who had negative skin tests to high concentrations of *Cladosporium herbarum* extract. All 16 had negative provocation tests. Extracts were made by the author. *Cladosporium herbarum* was cultured in liquid media, harvested, disintegrated, and extracted with 0.1 M sodium phosphate containing 0.015 M sodium citrate.

Pennington (Refs. 14 and 15) studied 11 patients with histories of hay fever and/or asthma who had manifestations of asthma or hay fever when *Cladosporium* (species not stated) mold spores or extracts were applied to the membranes of their nose and throat. All 11 had positive reactions to direct skin tests and 2 of 2 tested had positive reactions to passive transfer tests with *Cladosporium* extracts. In a routine survey of 215 allergy patients, these *Cladosporium* extracts produced positive skin reactions in 178 and negative reactions in 197. *Cladosporium* extracts were obtained from various sources; some were prepared in the authors laboratory, others were obtained from the Association of Allergists for Mycological Investigation and from unidentified commercial sources.

Brown (Ref. 22) mentioned a patient reported to him by Dr. Herbert Detweiler who grew tomatoes under glass which were heavily contaminated *Cladosporium fulvum*. He had attacks of asthma when harvesting the plants. "This patient was sensitive to the *Cladosporium fulvum* but not to the tomato plant, flower or fruit or anything else with which he was tested."

Bronsky and Ellis (Ref. 52) studied the reactions of 32 children to cutaneous and intracutaneous skin tests and bronchial challenge tests with a mixture of mold extracts containing *Alternaria, Cladosporium* (species not stated), Penicillum, and *Aspergillus*. Forty-two challenges were done in 31 patients. When the cutaneous test was positive, 77 percent of the bronchial challenges were positive. Where the intradermal test was positive, but the cutaneous test was negative, only 26 percent of the bronchial challenges were positive. All 10 challenges done in the presence of both negative cutaneous and intracutaneous tests were negative. Mold extracts were obtained from Center and Hollister-Stier Laboratories.

b. *Effectiveness of Cladosporium Extract for immunotherapy.* There are no controlled studies indicating the effectiveness of *Cladosporium* extract for reducing the severity of symptoms of hay fever and/or asthma induced by inhalation of *Cladosporium* spores. In view of the clinical impression from uncontrolled studies that this immunotherapy is effective (Refs. 5, 14, 21, and 23) and the general assumption that properly given immunotherapy with any specific allergen will reduce the severity of symptoms of asthma and/or hay fever due to the inhalation of that particular allergen, it would seem highly likely that suitable controlled studies would demonstrate the effectiveness of *Cladosporium* extract immunotherapy.

c. *Recommendations for Cladosporium extract.* (1) *Cladosporium* (*Hormodendrum*) extract is an effective aid for the diagnosis of hay fever and/or asthma induced by the inhalation of *Cladosporium* spores. In a patient with typical manifestations of hay fever and/or asthma after the inhalation of *Cladosporium* spores, a correctly interpreted positive skin reaction to a properly applied low dose of *Cladosporium* extract indicates that allergy to *Cladosporium* is at least one cause of the hay fever and/or asthma symptoms.

(2) Uncontrolled studies suggest that properly administered immunotherapy with *Cladosporium* extract may be an effective method for reducing the severity of symptoms of hay fever and/or asthma induced by inhalation of *Cladosporium* spores.

(3) The Panel recommends that *Cladosporium* extracts be placed in Category I for skin test diagnosis and in Category IIIA for immunotherapy.

3. *Helminthosporium.* *Helminthosporium* spores have been recovered from the outdoor air over a considerable portion of the United States. Although their distribution is wide, the counts in contrast to *Alternaria* and *Cladosporium* (*Hormodendrum*) have been generally low, and their occurrence sporadic. While spores may be found every month of the year in some southern states such as Texas, in some surveys they have been isolated most frequently in the South during the spring, summer and fall, and in the North only in the summer (Ref. 30). They may be found indoors and in one survey were found indoors commonly in September and October, and not found in the months between November and February (Ref. 10).

a. *Effectiveness of Helminthosporium extract for skin test diagnosis.* The reported evidence is scanty but uniformly indicates that a properly performed and interpreted skin test may be of value as an aid in the diagnosis of hay fever and/or asthma induced by inhalation of *Helminthosporium* spores, (Refs. 5 through 7).

Blumstein (Ref. 5) studied two patients who had hay fever and/or asthma in the *Helminthosporium* season and positive nasal reaction to dried powdered *Helminthosporium* (species not stated) pellicle. All had positive reactions to direct skin tests; probably one or two had positive reactions to passive transfer tests. Twenty-four additional patients with positive skin tests to *Helminthosporium* (species not stated) extracts had negative nasal challenge tests with dried, powdered

Helminthosporium pellicle. Three hundred and eighty patients had negative skin reactions to the *Helminthosporium* extract. The *Helminthosporium* extracts were made by the author. The mold was grown for 3 weeks in liquid peptone meat extract media. The pellicle was removed, killed in a sterilizing jar over 40 percent formalin, air dried, powdered, and extracted with Coca's solution.

Halpern, Holman, and Whittaker (Ref. 6) studied nine patients with hay fever and/or asthma who had positive reactions to nasal provocation tests with *Helminthosporium* (species not stated) extracts. All had positive reactions to skin tests with these extracts. Seven additional patients with hay fever and/or asthma had positive reactions to skin tests with *Helminthosporium* extracts but negative reactions to nasal provocation tests with *Helminthosporium* extracts. No skin tests in normal control subjects were reported. Extracts were either Type 33 extracts obtained from Hollister-Stier (Ref. 7) or standard extracts made by the authors by extracting dried powder of *Helminthosporium* obtained from "reliable commercial sources" in Hollister-Stier's solution.

Prince (Ref. 7) studied 42 patients who had been determined to be sensitive to *Helminthosporium* before the onset of the study mainly by demonstrating positive reactions to skin tests with other *Helminthosporium* extracts. All 42 had positive reactions to *Helminthosporium interseminatum* MMP extracts. (Eighty percent reacted to cutaneous tests with a 1:50 dilution, and 100 percent to intradermal tests with 1:1000 dilution or less.) On the other hand, 60 patients who had been determined to be insensitive to *Helminthosporium* before the onset of the study mainly by demonstrating negative reactions to skin tests with other *Helminthosporium* extracts usually had negative reactions to skin tests with *Helminthosporium interseminatum* MMP extracts (zero percent reacted to cutaneous tests with 1:50 dilution, and 36 percent reacted to intracutaneous tests with 1:1000 or less). *Helminthosporium interseminatum* extract was obtained from Hollister-Stier.

b. *Effectiveness of Helminthosporium Extract for immunotherapy.* There are no controlled studies indicating the effectiveness of *Helminthosporium* extract for reducing the severity of symptoms of hay fever and/or asthma induced by inhalation of *Helminthosporium* spores.

c. *Recommendations for Helminthosporium extract*—(1) *Helminthosporium* extract is an effective aid for the diagnosis of hay fever and/or asthma produced by inhaling of *Helminthosporium* spores. In a patient with typical manifestations of hay fever and/or asthma after inhaling *Helminthosporium* spores, a correctly interpreted positive skin reaction to a properly applied low dose of *Helminthosporium* extract indicates that allergy to *Helminthosporium* is at least one cause of the hay fever and/or asthma symptoms.

(2) Uncontrolled observations suggest that properly administered immunotherapy with *Helminthosporium* extract may be an effective method for reducing the severity of symptoms of hay fever and/or asthma induced by inhalation of *Helminthosporium* spores.

(3) The Panel recommends that *Helminthosporium* extracts be placed in Category I for skin test diagnosis, and in Category IIIA for immunotherapy.

4. *Aspergillus. Aspergillus* spores are consistently present in the outside air during most of the year, with occasional high spore counts at irregular intervals (Ref. 30). In the Puget Sound area, the highest counts occur in the season between May and October (Ref. 29). Indoors, it may grow under suitable conditions at any time of year (Refs. 10, 29, 31 and 40).

a. *Effectiveness of Aspergillus Extract for skin test diagnosis of hay fever and/or asthma induced by inhaling Aspergillus spores.* The reported evidence indicates that a properly performed and interpreted skin test may be of considerable value as a diagnostic aid (Refs. 6, 8, 14, 15, 28, 31, and 41).

There is insufficient evidence about which *Aspergillus* species should be used for skin testing. Most work has been done with *Aspergillus fumigatus*, either alone (Refs. 6, 14, 15, and 31) or in combination with other *Aspergillus* species (Ref. 41) *Aspergillus niger* has been used in one study (Ref. 8) and in another the species used were not described (Ref. 28). There is considerable cross reaction between various *Aspergillus* species extracts but all patients reacting to some species do not react to all (Refs. 5, 32, and 41). (See the section on Specificity in the introduction to mold extracts.)

Bernton (Ref. 31) studied one patient who had symptoms of asthma and hay fever when in moldy houses and after subcutaneous injection of *Aspergillus fumigatus* extract. The patient had a positive reaction to skin test with *Aspergillus fumigatus* extract. *Aspergillus fumigatus* extract was made by the author by extracting dried, powdered, *Aspergillus fumigatus* pelts.

Halpern, Holman, and Whittaker (Ref. 6) studied one patient with rhinitis who had a positive reaction to nasal provocation test with *Aspergillus* (species not stated) extracts. The patient had a positive reaction to skin test with *Aspergillus* extract. Ten additional patients with rhinitis had positive reactions to skin tests with *Aspergillus* extract, but negative or equivocal reactions to nasal provocation tests with these extracts.

Ripe (Ref. 8) studied 36 patients with rhinitis and/or asthma who had positive reactions to skin tests with *Aspergillus niger* extracts. Nasal or bronchial provocation tests were positive in 12 of the 36, and in 4 of 6 of those whose skin reacted to low concentrations of the extract. In addition, he studied 10 patients who had negative skin reactions to high concentrations of *Aspergillus niger* extract. Six of these had negative or equivocal reactions, but 4 had positive reactions to nasal or bronchial provocation tests. Extracts were made by the author. *Aspergillus niger* was cultured in liquid media, harvested, disintegrated, and extracted with 0.1 M sodium phosphate containing 0.015 M sodium citrate.

Pennington (Refs. 14 and 15) studied one patient with a history of asthma who had manifestations of hay fever when *Aspergillus ochrochus* mold spores were applied to the membranes of the nose and throat. The patient had a positive reaction to skin test with *Aspergillus ochrochus* extract. *Aspergillus ochrochus* extract was prepared by the author by adding 10 grams (g) of "dried mold" to 100 mL of "extracting fluid."

Colen, Van Arsdel, Pasnick, and Horan (Ref. 28) studied six patients with a history of asthma which increased in severity during the *Aspergillus* season, who had positive reactions to bronchial challenge tests with *Aspergillus* (species not stated) extracts. All six had positive reactions to both direct skin and passive transfer tests with *Aspergillus* extracts. Bronchial challenge tests with these extracts were negative in three additional patients who had a history of asthma who had positive reactions to skin tests with *Aspergillus* extract, and of whom two were tested showing positive reactions to passive transfer tests with this extract. *Aspergillus* extract was obtained from Hollister-Stier Laboratories.

Weiner (Ref. 41) described one patient who developed asthma when in a bakery contaminated with *Aspergillus* (species not stated) spores and after sniffing *Aspergillus fumigatus* spores from the end of a tooth pick. The patient

had positive reactions to both direct skin and passive transfer tests with extracts of *Aspergillus fumigatus*. *Aspergillus fumigatus* extracts were obtained from Hollister-Stier Laboratories.

b. *Effectiveness of Aspergillus extract for immunotherapy.* There are no controlled studies which indicate the effectiveness of immunotherapy with *Aspergillus* extract for reducing the severity of symptoms of hay fever and/or asthma induced by inhalation of *Aspergillus* spores.

Therefore, there is no conclusive proof of the effectiveness of *Aspergillus* extract immunotherapy. In view of the clinical impression from uncontrolled observations that this immunotherapy is effective (Refs. 14, 28, and 41) and the general assumption that properly given immunotherapy with any specific allergen will reduce the severity of symptoms of asthma and/or hay fever due to the inhalation of that particular allergen, it would seem highly likely that suitable controlled studies would demonstrate the effectiveness of *Aspergillus* extract immunotherapy.

c. *Effectiveness of Aspergillus fumigatus extract for skin test diagnosis of allergic bronchopulmonary aspergillosis.* The reported evidence indicates that a properly performed and interpreted skin test may be of considerable value as a diagnostic aid in allergic bronchopulmonary aspergillosis (Refs. 32 through 39). The following points must be considered:

The clinical diagnosis of allergic bronchopulmonary aspergillosis must be firmly established. Allergic bronchopulmonary aspergillosis is a syndrome characterized by asthma, transient pulmonary infiltrates, blood and sputum eosinophilia, *Aspergillus fumigatus* in sputum, IgE antibodies to *Aspergillus fumigatus* extract, and IgG antibodies to *Aspergillus fumigatus* extract (Refs. 32, and 34 through 39).

These patients have *Aspergillus fumigatus* actively growing in the lumena of their bronchopulmonary tract without invasion of tissue. The episodes of asthma and pulmonary consolidation are presumed to be mediated by the combined action of the IgE and IgG antibodies to *Aspergillus fumigatus*. When the appropriate manifestations are present, a diagnosis of allergic bronchopulmonary aspergillosis can be established with considerable accuracy.

Cutaneous or intradermal skin testing with *Aspergillus fumigatus* extract is the commonly used method for demonstrating IgE antibodies to that allergen (Refs. 32 through 40). A typical wheal and erythema reaction 15 minutes after applying the test is an indication of IgE antibodies to *Aspergillus fumigatus* extract. Additional evidence of IgE antibodies to this extract has been obtained by demonstrating passive transfer of immediate skin reactivity to this extract to the skin of humans (Refs. 34 and 39) and monkeys (Refs. 38 and 40) elimination of patient's serum's capacity to transfer immediate skin reactivity to this extract by treating the serum with IgE immunoabsorbent (Ref. 34) and clinical asthma and/or reduction in expiratory flow rates after bronchial provocation tests with *Aspergillus fumigatus* extract (Refs. 32, 37, and 39).

Intradermal skin testing with Aspergillus fumigatus extract has also been used to demonstrate IgG antibodies to that allergen. Erythema and induration appearing 2 to 3 hours after application of the test and lasting about 24 hours may be an indication of IgG antibodies to the extract (Refs. 32, 34, 36, 38, and 39). This has been termed the "late reaction" to distinguish it from the "immediate reaction" manifested by wheal and erythema which occurs 15 minutes after application of the test. The immediate reaction may subside before the late reaction commences to produce a "dual reaction." "dual reaction." IgG antibodies to *Aspergillus fumigatus* extract may be demonstrated more definitively by demonstrating precipitating antibody to *Aspergillus fumigatus* extract by use of double diffusion technique (Refs. 32, and 34 through 40) and by demonstrating passive cutaneous anaphylaxis to *Aspergillus fumigatus* extract in guinea pigs sensitized by intradermal injections of patients serum and challenged intravenously with *Aspergillus fumigatus* extract and Evans blue dye (Refs. 38 and 39).

Aspergillus fumigatus extracts used for skin testing patients with bronchopulmonary aspergillosis have usually been obtained from commercial sources (Refs. 32 through 35) and little information is given about their preparation. Where preparation has been described, they have been prepared by both the regular (Refs. 33, 37, and 38) and MMP (Ref. 33) processes described earlier. Extracts prepared by either process and commercial extracts have produced satisfactory skin reactions in sensitive patients (Refs. 32 through 39).

Irritative reactions must be differentiated from specific reactions. This point is discussed in the mold extract introduction.

Clinically sensitive patients who have allergic bronchopulmonary aspergillosis have positive skin reactions to *Aspergillus fumigatus* extract but do not have equal skin reactivity. Most will react to low doses of *Aspergillus fumigatus* extract; a few will react to high doses only (Ref. 32).

Patients who do not have allergic bronchopulmonary aspergillosis may nevertheless have skin reactions to Aspergillus fumigatus extract. Patients with hay fever and/or asthma after exposure to *Aspergillus fumigatus* spores, but without allergic bronchopulmonary aspergillosis will have positive skin tests to *Aspergillus fumigatus* extract as discussed in the preceeding section. In addition many atopic patients clinically free of symptoms after exposure to *Aspergillus fumigatus* spores but with asthma and/or hay fever symptoms induced by exposure to allergens other than *Aspergillus fumigatus* (henceforth called clinically insensitive patients) will have a positive skin reaction to *Aspergillus fumigatus* extract (Refs. 6, 8, and 24). This type of clinically insensitive patient commonly is "less skin reactive" than the clinically sensitive patient in that higher doses on the average are needed to elicit the reaction. Nevertheless, there are some clinically insensitive patients who react to low doses of the extract, and some clinically sensitive patients who only react to high doses so that there is overlap, and, therefore, a positive skin reaction to a certain concentration of *Aspergillus fumigatus* extract by itself is not diagnostic of allergic bronchopulmonary aspergillosis.

The presence of both skin reaction to *Aspergillus fumigatus* extract and the other components of the syndrome listed above is usually diagnostic of allergic bronchopulmonary aspergillosis.

Goldstein and Yokayama (Ref. 34) studied one patient with allergic bronchopulmonary aspergillosis who had asthma, eosinophilia, pulmonary infiltrates, and precipitin reactions to *Aspergillus fumigatus* extracts. The patient had positive reactions to both direct skin and passive transfer tests with *Aspergillus fumigatus* extracts. The precipitin antibody was shown to be IgG by gel diffusion analysis. The passive transfer antibody (reagin) was shown to be IgE by adsorbtion with IgE immunoadsorbent. *Aspergillus fumigatus* extract was obtained from Hollister-Stier Laboratories.

Henderson (Ref. 35) studied 22 patients with allergic bronchopulmonary aspergillosis who had asthma, eosinophilia, pulmonary infiltrates, and *Aspergillus fumigatus* in the sputum. All had positive precipitin tests to *Aspergillus fumigatus*. All had positive reactions to skin tests with *Aspergillus fumigatus* extracts. No skin tests in control patients were reported.

Aspergillus fumigatus extract was obtained from Bencard Laboratories.

Warren and Rose (Ref. 36) studied seven patients with allergic bronchopulmonary aspergillosis who had asthma, eosinophilia, pulmonary infiltrates, and *Aspergillus fumigatus* in the sputum. All had positive immediate and late reactions to intradermal tests with *Aspergillus fumigatus* extracts. No skin tests in control patients were reported.

Stevens, Hilvering, and Orie (Ref. 37) studied two patients with allergic bronchopulmonary aspergillosis who had asthma, eosinophilia, pulmonary infiltrates, and *Aspergillus fumigatus* in the sputum. All had positive reactions to skin, bronchial challenge, and precipitin tests with *Aspergillus fumigatus* extracts. No skin tests in control patients were reported. *Aspergillus fumigatus* extracts were made by the authors. The mold was grown in liquid media, harvested, ground with carborundum in an agate mortar, and extracted with distilled water.

Golbert and Paterson (Ref. 38) studied one patient with allergic bronchopulmonary aspergillosis who had asthma, eosinophilia, pulmonary infiltrates, and *Aspergillus fumigatus* in the sputum. The patient had positive reactions to direct skin, passive transfer, and precipitin tests with *Aspergillus fumigatus* extracts. A rehesus monkey was given serum from this patient intravenously. When the monkey was subjected to bronchial challenge test with *Aspergillus fumigatus* extract, the monkey developed pulmonary infiltrates consisting of nodular accumulations of eosinophils, neutrophils, and round cells. No skin tests in control patients were reported. *Aspergillus fumigatus* extracts were prepared by the authors using a strain isolated from the patient's sputum. The mold was cultured for 3 weeks in liquid media, harvested, washed, dried, powdered, and extracted.

Slavin, Stanczky, Lonigro, and Broun (Ref. 39) studied one patient with allergic bronchopulmonary aspergillosis who had asthma, esosinophilia, pulmonary infiltrates, and *Aspergillus fumigatus* in the sputum. The patient had positive reactions to direct skin, passive transfer, bronchial challenge, and precipitin tests with *Aspergillus fumigatus* extracts. No skin tests, in control patients were reported. *Aspergillus fumigatus* extract was obtained from Abbott Laboratories.

McCarthy and Pepys (Ref. 32) studied 111 patients with allergic bronchopulmonary aspergillosis who had all or most of the characteristic manifestations which include asthma, eosinophilla, pulmonary infiltrates, and *Aspergillus fumigatus* in the sputum. All had positive reactions to skin tests with *Aspergillus fumigatus* extract. Five of 5 had positive reactions to nasal challenge tests, and 20 of 21 had positive reactions to bronchial challenge tests and 71 of 99 had positive precipitin tests with this extract. Eleven control patients had negative reactions to skin and bronchial challenge tests with these extracts. *Aspergillus fumigatus* extract was obtained from Bencard Laboratories.

Argabrite, Morrow, and Meyer (Ref. 33) studied one patient with allergic bronchopulmonary aspergillosis who had asthma, eosinophilia, pulmonary infiltrates, and *Aspergillus fumigatus* in his sputum. This patient had a positive reaction to skin test with both Type 33 and MMP *Aspergillus fumigatus* extracts. No skin tests in control patients were described.

Slavin, Laird, and Cherry (Ref. 40) studies one child with allergic bronchopulmonary aspergillosis who had asthma, eosinophila, pulmonary infiltrates, and *Aspergillus fumigatus* in the sputum. She had positive reactions to direct skin, passive transfer and precipitin tests with *Aspergillus fumigatus* extract. No skin tests in control subjects were described.

d. *Effectiveness of Aspergillus Fumigatus extract for immunotherpy of patients with allergic bronchopulmonary aspergillosis.* There are no controlled studies indicating the effectiveness of immunotherpy with *Aspergillus fumigatus* extract for reducing the severity of symptoms from allergic bronchopulmonary aspergillosis. McCarthy and Pepys have stated in their article reporting their vast experience with 111 cases that "specific immunologic treatment by attempts at hyposensitization is unsatisfactory because of the local and asthmatic reactions, presumed to be of a Type III nature, which are provoked" (Ref. 32). Similar problems were noted by Warren and Ross (Ref. 36) who stated:

> Although injections of *Aspergillus fumigatus* are well tolerated by asthmatic patients, the majority of patients with this sydrome react adversely, giving increasingly large local and occasionally late systemic reactions, even when the concentration of extract used is very low.

There is one report (Ref. 33) of a patient with asthma, transient pulmonary infiltrates, eosinophilia, *Aspergillus fumigatus* in the sputum, and postive skin test to *Aspergillus* fumigatus extract who had improvement after, and no untoward effects from, immunotherapy with *Aspergillus fumigatus* extract. However, no studies to demonstrate precipitating antibody to *Aspergillus fumigatus* extract were done, and it is possible that the favorable effects noted were due to the absence of precipitins needed to mediate a Type- III reaction.

e. *Recommendations for Aspergillus extracts*—(1) *Aspergillus* extract is an effective aid for the diagnosis of hay fever and/or asthma induced by inhaling *Aspergillus* spores. In a patient with typical manifestations of hay fever and/or asthma after inhaling *Aspergillus* spores, a correctly interpreted positive skin reaction to a properly applied low dose of *Aspergillus* extract indicates that allergy to *Aspergillus* is at least one cause of the hay fever and/or asthma symptoms.

(2) Uncontrolled clinical observations suggest that properly administered immunotherapy with *Aspergillus* extract may be an effective method for reducing the severity of symptoms of hay fever and/or asthma induced by inhaling *Aspergillus* spores.

(3) *Aspergillus fumigatus* extract is an effective aid for the diagnosis of allergic bronchopulmonary aspergillosis. In a patient with asthma, transient pulmonary infiltrates, eosinophila in blood and sputum, *Aspergillus fumigatus* in sputum, and precipitating antibodies to *Aspergillus fumigatus* extract, a correctly interpreted positive skin reaction to a properly applied low dose of *Aspergillus fumigatus* extract indicates that the patient has allergic bronchopulmonary aspergillosis.

(4) *Aspergillus fumigatus* extract is not recommended for immunotherapy of allergic bronchopulmonary aspergillosis because local and asthmatic reactions frequently follow injections of this extract for this purpose.

(5) The Panel recommends that *Aspergillus* extracts be placed in Category I for skin test diagnosis, in Category IIIA for immunotherapy of asthma and rhinitis, and in Category II for immunotherapy of bronchopulmonary aspergillosis.

5. *Penicillium.* Outdoors, *Penicillium* spores are consistently present in the air during most of the year, with occasional high spore counts at irregular intervals (Ref. 30). In the Puget Sound area, the highest counts occur in the season between May and October (Ref. 29). Indoors, it may grow under suitable conditions at any time of year (Refs. 10, 24 and 29).

a. *Effectiveness of Penicillium extract for skin test diagnosis.* The reported evidence indicates that a properly performed and interpreted skin test may be of considerable value as an aid in the

diagnosis of hay fever and/or asthma induced by inhalation of *Penicillium* spores (Refs. 6, 8, 14, 15, 24, and 26 through 28).

Ramirez and Eller (Ref. 26) studied one patient who had asthma and urticaria when in room air containing *Penicillium* spores. Direct skin tests and passive transfer tests with *Penicillium* extracts (species not stated) were positive.

Jimenez-Dias, Cuenca, and Puig (Ref. 27) studied one patient who had asthma when sleeping on a pillow which had been sprayed with a *Penicillium glaucum* culture. Direct skin and passive transfer tests with *Penicillium glaucum* extracts were positive.

Colen, Van Arsdel, Pasnick, and Horan (Ref. 28) studied six patients who had positive reactions to bronchial challenge tests with *Penicillium* extract (species not stated). All six had positive reactions to skin tests with *Penicillium* extracts. Serum from five of the six patients also produced positive passive transfer tests. An additional three patients had positive reactions to skin tests but negative reactions to bronchial challenge tests with *Penicillium* extracts. The *Penicillium* extracts were obtained from Hollister-Stier.

Halpern, Holman, and Whittaker (Ref. 6) studied two patients with rhinitis and/or asthma who had positive reactions to nasal provocation tests with *Penicillium* extract (species not stated). All had positive reactions to skin tests with these extracts. Five additional patients with rhinitis and/or asthma had positive reactions to skin tests with *Penicillium* extracts but negative reactions to nasal provocation tests with *Penicillium* extracts. No skin tests in normal control subjects were reported.

Ripe (Ref. 8) studied 38 patients with asthma and/or rhinitis who had positive reactions to skin tests with *Penicillium frequentans* extract. Nasal or bronchial provocation tests were positive in 15 of the 38, and in 5 of 6 of those whose skin reacted to very low concentrations of this extract. In addition, he studied seven patients with asthma and/or rhinitis who had negative skin tests to high concentrations of *Penicillium frequentans* extract. All seven had negative nasal or bronchial provocation tests. Extracts were made by the author. *Penicillium frequentans* was cultured in liquid media, harvested, disintegrated, and extracted with 0.1 M sodium phosphate containing 0.15 M sodium citrate.

Pennington (Refs. 14 and 15) studied one patient with asthma and hay fever, who developed symptoms of his allergic disease when *Penicillium rubrum* spores were applied to the membranes of his nose and throat, and who had a positive reaction to skin test with *Penicillium rubrum* extract. In a routine survey of 160 allergy patients, these *Penicillium rubrum* extracts produced positive skin reactions in 60 patients and negative skin reactions in 100 patients.

Bronsky and Ellis (Ref. 52) studied the reactions of 32 children to cutaneous and intracutaneous skin tests and bronchial challenge tests with a mixture of mold extracts containing *Alternaria, Cladosporium, Penicillium* (species not stated) and *Aspergillus*. Forty-two challenges were done in 31 patients. When the cutaneous test was positive, 77 percent of the bronchial challenges were positive. When the intradermal test was positive, but the cutaneous test was negative, only 26 percent of the bronchial challenges were positive. All 10 challenges done in the presence of both negative cutaneous and intracutaneous tests were negative. Mold extracts were obtained from Center, Hollister-Stier, or Endo Laboratories.

(b) *Effectiveness of Penicillium extract for immunotherapy.* There are no controlled studies indicating the effectiveness of *Penicillium* extract for reducing the severity of symptoms of hay fever and/or asthma induced by inhalation of *Penicillium* spores.

There is the clinical impression from uncontrolled studies that this immunotherapy is effective (Refs. 14 and 28).

c. *Recommendations for Penicillium extracts.* The Panel recommends that *Penicillium* extracts be placed in Category I for skin test diagnosis, and in Category IIIA for immunotherapy.

6. *Mucor. Mucor* spores have been recovered from outdoor air over a considerable portion of the United States. Although their distribution is wide, the counts in contrast to *Alternaria* and *Cladosporium (Hormodendrum)* have been generally very low and their occurrence sporadic. They have been found somewhat more frequently in the South, but not consistently in any region (Ref. 30). They may be found indoors (Ref. 42).

a. *Effectiveness of Mucor extract for skin test diagnosis.* The reported evidence is scanty but uniformly indicates that a properly performed and interpreted skin test may be of value as an aid in the diagnosis of hay fever and/or asthma induced by inhalation of Mucor spores (Refs. 5, 8, 14, 15 and 42).

Flood (Ref. 42) studied one patient with a history of asthma and hay fever who developed typical manifestations of asthma when challenged by an intranasal and intraoral spray with a filtrate of *Mucor plumbeus*. This patient had a positive reaction to skin test with *Mucor plumbeus* extract. The extracts were made by the author by taking the pellicle from an old *Mucor plumbeus* culture, washing it, grinding it with carbon dioxide snow and sand, and extracting the mold powder with phenol saline.

Blumstein (Ref. 5) studied one patient with hay fever and/or asthma in the *Mucor* season and positive nasal reaction to dried, powdered *Mucor* pellicle (species not stated). This patient had a positive reaction to skin test with *Mucor* extract (species not stated). Skin tests with *Mucor* extracts were negative in 366 allergic patients. Thirty-nine additional patients with positive reactions to skin tests with *Mucor* extracts had negative nasal challenge tests with dried, powdered *Mucor* pellicle. The *Mucor* extracts were made by the author. The mold was grown for 3 weeks in liquid peptone meat extract media. The pellicle was removed, killed in a sterilizing jar over 40 percent formalin, air dried, ground to a fine powder, and extracted with Coca's solution.

Ripe (Ref. 8) studied 22 patients with symptoms of rhinitis or asthma who had positive skin tests of *Mucor hiemalis* extracts. Nasal or bronchial provocation tests were positive in 17 of the 22, and in 11 of 11 of those whose skin reacted to low concentrations of the extract. In addition, he studied six patients with rhinitis or asthma who had negative reactions to skin tests with high concentrations of *Mucor hiemalis* extract. All six had negative bronchial or nasal provocation tests. Extracts were made by the author. *Mucor hiemalis* was cultured in liquid media, harvested, disintegrated, and extracted with 0.1 M sodium phosphate containing 0.015 M sodium citrate.

Pennington (Refs. 14 and 15) studied four patients with a history of hay fever and/or asthma who had manifestations of hayfever when *Mucor* (species not stated) mold spores were applied to the membranes of their nose and throat. All four had positive reactions to skin tests with *Mucor* extracts. Passive transfer test was attempted in one of these patients and was negative. In a skin test survey of 539 patients with a history of asthma and/or hay fever these *Mucor* extracts produced positive reactions in 163 patients and negative reactions in 376 patients.

b. *Effectiveness of Mucor extract for immunotherapy.* There are no controlled studies indicating the effectiveness of *Mucor* extract for reducing the severity of symptoms of hay fever and/or asthma induced by inhalation of *Mucor* spores.

There is the clinical impression from uncontrolled observations that this immunotherapy is effective.

c. *Recommendations for Mucor extract.* The Panel recommends that *Mucor* extracts be placed in Category I for skin test diagnosis, and in Category IIIA for immunotherapy.

7. *Botrytis, Candida Albicans, Cephalothecium Roseum, Monilia Sitophilia and Pullularia.* Outdoors, these spores may be present in the air during all or part of the year, with occasional high spore counts at irregular intervals (Refs. 43 and 44). Indoors, they may grow under suitable conditions at any time of year (Ref. 44).

a. *Effectiveness for skin test diagnosis.* Ripe (Ref. 8) studied 43 patients with symptoms of rhinitis or asthma who had positive skin tests to *Botrytis cineria* extracts. Nasal or bronchial provocation tests with these extracts were positive in 24 of the 43, and in 6 of 6 of those whose skin reacted to low concentrations of the extract. In addition they studied six patients with rhinitis or asthma who had negative reactions to skin tests with high concentrations of *Botrytis cinera* extract. Five had negative, and one positive, bronchial or nasal provocation tests. The extracts were made by the author. *Botrytis cineria* was cultured in liquid media, harvested, disintegrated, and extracted with 0.1 M sodium phosphate containing 0.015 M sodium citrate.

Itkin and Dennis (Ref. 45) studied 42 patients with a history of asthma who had positive reactions to intradermal tests with a 1:1000 w/v dilution of *Candida albicans* extract. Twenty-four of the 42 had positive reactions to bronchial provocation tests with these extracts. They also studied 23 patients who had negative skin tests to this extract. Five of the 23 had positive reactions to bronchial provocation tests with this extract. The sera of three patients who had immediate direct positive skin reactions to a 1:1,000 w/v dilution of *Candida albicans* extract and positive bronchial reactivity were able to achieve passive sensitization of the skin of normal individuals to the same extract. *Candida albicans* extract was obtained from Hollister-Stier.

Pennington (Refs. 14 and 15) studied two patients with a history of asthma or hay fever who developed symptoms of hay fever when *Cephalothecium roseum* spores were applied to the membranes of the nose and throat. Both had positive reactions to skin tests with *Cephalothecium roseum* extracts. An additional patient was reported who had a history of asthma and who had a positive reaction to skin test with *Cephalothecium roseum* extracts, but who developed no symptoms when *Cephalothecium roseum* spores were applied to the membranes of the nose and throat. A skin test survey of 160 patients with hay fever of asthma demonstrated that 47 had positive and 113 negative reactions to these *Cephalothecium roseum* extracts. The extracts were obtained from an unidentified commercial source.

Pennington (Refs. 14 and 15) studied three patients who had a history of asthma or hay fever and who had symptoms of hay fever when *Monilia sitophilia* spores were applied to the membranes of the nose and throat. All had positive reactions to direct skin tests, and one of one tested had positive reaction to passive transfer test with *Monilia sitophilia* extract. In a skin test survey of 526 patients with hay fever or asthma, 616 tests were done with various *Monilia sitophilia* extracts, and positive reactions were obtained in 206, and negative reactions were obtained in 410. Some *Monilia sitophilia* extracts were prepared by the author by extracting dried mold with extracting fluid; others were obtained from unidentified commercial sources.

Blumstein (Ref. 5) studied three patients who had symptoms of hay fever and/or asthma in the *Monilia sitophilia* season, and who had positive reactions to nasal provocation tests with dried, powdered *Monilia sitophilia* pellicle. All had positive reactions to direct skin tests and some had positive reactions to passive transfer tests with these extracts. Thirty additional patients with positive reactions to skin tests with this extract had negative reactions to nasal provocation tests with dried powdered *Monilia sitophilia* pellicle. Four-hundred and six patients were tested with these extracts: 33 gave positive reactions and 373 gave negative reactions. The *Monilia sitophilia* extract was prepared by the author. The mold was grown for 3 weeks in liquid peptone meat extract media. The pellicle was removed, killed in a sterilizing jar over 40 percent formalin, air dried, powdered, and extracted with Coca's solution.

Ripe (Ref. 8) studied 55 patients with a history of asthma and/or rhinitis who had positive reactions to skin tests with *Pullularia pullulans* extracts. Nasal or bronchial provocation test with these extracts were positive in 32 of the 55, and in 12 of 12 of those whose skin reacted to low concentrations of the extract. In addition, he studied one patient with asthma and/or rhinitis who had negative reaction to skin test with high concentration of the extract and who had negative reaction to nasal and bronchial provocation tests. The extract was made by the author. *Pullularia pullulans* was cultured in liquid media, harvested, disintegrated, and extracted with 0.1 M sodium phosphate containing 0.015 M sodium citrate.

b. *Effectiveness for immunotherapy.* There are no controlled studies indicating the effectiveness of immuntherapy with extracts of *Botrytis cineria, Candida albicans, Cephalothecium roseum, Monilia sitophila,* or *Pullaria pullulans.*

c. *Recommendations.* The Panel recommends that these five extracts be placed in Category IIIA for both skin test diagnosis and immunotherapy of patients with hay fever and/or asthma induced by exposure to the specific mold spores.

8. *Mold extracts for fungal infections and dermal allergic sensitivity. Candida (monilia) albicans* extracts and *Trichophyton* extracts are among the products which have been licensed as allergenic extracts and labeled for use in skin testing and treatment of patients infected with or having dermal sensitivity to *Candida albicans, trychophytons* and similar fungi. The labeling for most of the following mold extracts do not clearly define the diseases or allergic conditions for which they are intended. Their effectiveness in the diagnosis and treatment of these diseases has never been established, chiefly because of the almost universal incidence of immunologic experience with these organisms, an adventitious fact that makes these extracts useful in cell-mediated immune deficiency testing.

Product Reviews of Extracts of Molds Involved in Dermatomycosis

a. *Product descriptions—(1) Hollister-Stier Laboratories, Division of Cutter Laboratories, Inc., products* Dermatophytin™ is composed the combined broth filtrates of three species of *Trichophyton* cultures, each grown separately. These are *T. purpurum, T. gypseum,* and *T. interdigitale.* Dermatophytin is sold undiluted, as a 1:30 dilution and as a dilution series.

Dermatophytin"O"™ is composed of the broth filtrate of *Candida albicans* mycelial mats. Dermatophytin "O" is sold undiluted, at a 1:100 dilution and in a dilution series. Hollister-Steir also produces "T.O.E." (*C. albicans* (Oidiomycin), *Trichophyton mix, Epidermophyton floccosum,* and *Microsporum*) mix made by their "regulator process" described earlier in this report.

(2) *Antigen Laborabories, Inc., product.* Antigen Laboratories' T.O.E. Allergenic Extract (trichophyton,

oidiomycin and epidermophyton) consists, according to the labeling, of *Trichophyton interdigitale* 0.166 per cent, *T. rubrum* 0.166 per cent, *Monilia albicane* 0.333 per cent, and *Epidermophyton inguinale* 0.333 per cent with 50 percent glycerin in a phenolated buffered saline solution.

(3) *Other manufacturers.* Among the molds implicated in dermatomycosis, several manufacrurers sell extracts such as *Candida albicans, Epicoccum purpurascens, Microsporum canis, Trichophyton mentagrophytes, T. rubrum, T. violaceum* and *schoenleinii.* These extracts are manufactured by the same methods and the same source materials are used as for the other mold extracts sold by the firm for use in inhalant allergy.

b. *Standarization.* Standarization is either by weight to volume, PNU or in one instance, gross bio-activity as ascertained by skin testing known positive patients. The latter statement is made generally for "mold and smit" products, rather than for these extracts specifically.

c. *Recommended use/indication—Hollister-Stier Laboratories.* Diagnosis: Dermatophytin and Dermatophytin "O" are labeled for use in delayed hypersensitivity skin testing (with the test site to be read at 24 to 72 hours) presumably to detect the presence of infection with the offending organism. No recommendations for immediate hypersensitivity skin testing are given.

Treatment: Treatment for dermatomycosis by desensitization is given in the labeling for Dermatophytin and Dermatophyton "O". T.O.E. (Tricophyton, Oidiomycin (i.e., Candida), Epidermophyton) is offered for desensitization of various "fungal dermatitis".

2 *Antigen Laboratories.* Antigen Laboratories' labeling mentions pathogenic fungal infections and "if" reactions in the skin. The product is labeled for skin test diagnosis by an end point titration method and for treatment to achieve clinical relief of symptoms.

3 *Other manufacturers.* Only general labeling for use in asthma or hay fever similar to that for pollens, epidermals and other inhalants was submitted for extracts of dermatophytic molds. Nothing specific pertaining to the use of extracts of the dermatophytic molds was submitted.

d. *Critique*—(1) *Manufacture and standardization.* First it is clear that the producers use varying methods of production of the dermatophytic extracts. Two major variations are: (1) The nature of the nutrient media, whether it is totally synthetic or whether it also contains "natural products", some of which may themselves be allergenic; and (2) whether mycelial mat alone, broth alone, or both are used to make the extract. Other factors which are less important also exist. In addition, different genera and species of dermatophytes are made available by each company. Several species are common isolates from superficial fungus infections of the skin. Some of these are *T. rubrum, T. metagrophytes, C. albicans, M. canis, M. audouini,* and *E. floccosum.* Somewhat less common are *M. gypseum* and *T. tonsurans.* Many of these are not represented in the various extracts. For example Dermatophytin™ is made from *T. rubrum, T. mentagrophytes,* and *T. interdigitale.* It lacks the *Microsporum* species and *Epidermophyton.* If these extracts are indeed effective in diagnosis and/or therapy, all important allergens should be represented. Basically no standarization is used for each lot of extract but a bio-assay standardization should be possible by skin test in sensitive persons.

(2) *Effectiveness for diagnosis and therapy.* No data were found by the Panel, nor were any presented by the manufacturers establishing that these materials are effective in diagnosis or therapy of chronic fungal infections, fungal skin allergy conditions, or other disorders. Skin test surveys demonstrate that the majority of the population reacts positively to skin tests with one or more of the mold extracts, most of such reactions being the delayed type. Some patients, however, do respond with an immediate-type reaction.

(3) *Safety.* No untoward reactions to these extracts have been reported; however, the use of a 0.1 mL intradermal injection of a concentrated solution of *C. albicans* or *Trichophyton* extracts (as a test for delayed hypersensitivity) is liable to be unsafe in those few patients who have a high titer of reagins specific for allergens contained in these extracts. Those individuals could be at risk of an anaphylactic allergic reaction.

(4) *Use of the extracts.* Although the data supporting the use of *Candida albicans, Trichophyton,* and *Epidermophyton* extracts in diagnosis and treatment of infections are lacking, the high rate of cell-mediated hypersensitivity to one of more of a battery of these and other antigens in the general population of adults has made tests for delayed hypersensitivity to them to be of value in testing the immunocompetence of the T-cell system. Candidin and trichophyton when used in conjunction with a battery of other test agents for delayed hypersensitivity are an aid in such diagnosis. None of these extracts are standardized or labeled for use in determining immunocompetence. This use is discussed in the section on skin testing for cell-mediated immunity.

(5) *Recommendations*—(a) Extracts of molds employed in dermatomycoses should be placed in Category IIIB for diagnosis and treatment of active or latent dermatomycoses.

(b) *Candida* and *Trichophyton* extracts should be placed in Category IIIA for delayed hypersensitivity testing for immunocompetence. It is further recommended that the extracts be subjected to clincial and chemical tests to establish their safety, effectiveness, specificity, potency and purity.

(c) As with all products, the labeling should clearly identify the diseases or conditions for which they are intended.

9. *Rust, smut, and other basidiomycete extracts.* One of the earliest references to grain must causing allergic symptoms is the report of Wittich and Stakman in 1937 (Ref. 61) showing the presence of corn smut in the sputum of an asthmatic patient who also gave convincing skin reactions to corn and other grain smut extracts. Wittich presumes efficacy in treatment. Subsequently, not much has appeared in the literature in the form of similar case reports. Warren et al. (Ref. 62) present data showing 2 out of 10 grain workers giving immediate skin reactions to grain smut.

Lopez, et al. (Ref. 63), in 1973, compared skin test and RAST findings to a number of mushroom fungi spores in atopic individuals. It is evident that IgE-mediated reactions do occur to antigens of these spores. Kramer (Ref. 64) has shown a high incidence of such spores in the atmosphere in wooded areas during night time hours; but personal communication with him permits the conclusion that distribution is not widespread. Therefore, in spite of the high spore content of the air in certain areas under certain conditions, a large segment of the population would probably not be exposed. Kramer also feels that grain rust and smut have a more widespread distribution in areas where wheat and milo are grown extensively; but, while these spores could be an individual problem as in an occupational exposure or in other special situations, the general population would not be heavily exposed. Even though the grain smut and mushroom spores are small in size, have buoyancy, and can be found in high altitude almost world-wide (including the Polar caps), they are not found in high concentration at nose level very far from the point of origin (Ref. 65).

Hyde, (Ref. 66) in 1972, reviews and revises Thommen's postulates about pollen allergy (Ref. 67) with spores in mind.

Thommen's postulates:

1. The pollen must contain an excitant of hay fever.
2. The pollen must be anemophilous.
3. The pollen must be produced in sufficiently large quantities.
4. The pollen must be sufficiently buoyant to be carried considerable distances.
5. The plant producing the pollen must be widely and abundantly distributed.

Hyde's revision:

1. The pollen or other spore type must contain an excitant of hay fever or asthma.
2. The spore must be produced in sufficiently large quantities.
3. The spores must be sufficiently buoyant to become airborne.
4. The plant species must be widely and abundantly distributed.
5. In order that any type of spore shall be regarded as the causative agent in a particular case of hay fever or asthma, it must be shown that the patient experienced symptoms at a time or times when the spores concerned were present in large quantities in the air.

It has been demonstrated that a variety of grain rusts and smuts will produce allergic reactions. Species so identified are:

Wheat smut—*Tilletia tritici*
Tilletia levis
Ustilago tritici
Barley smut—*Ustilago bordei*
Ustilago nuda
Oat smut—*Ustilago avenae*
Rye smut—*Urocystis occulta*
Sorghum smut—*Sphacelotheca sorghi*
Sphacelotheca cruenta
Millet smut—*Ustilago crameri*
Corn smut—*Ustilago zeae*
Rust—*Puccinia graminis tritici*

A lesser number of mushroom spores have been similarly identified:

Mushroom—*Cantharellus, Coprinus, Frustulatum, Hypholoma, Pleurotus*
Jelly fungus—*Dacromyces*
Yeast—*Tilletiopsis*

All of the above are members of the *Basidiomycetes* class which is estimated to contain between 20,000 and 25,000 species. It is apparent that a considerable amount of work needs to be done before it is possible to establish the relative importance of the role of many of the *Basidiomycetes* species in the diagnosis and treatment of allergic diseases. Based on current knowledge, it would appear that certain spores of the *Basidiomycetes* class are important allergens to some individuals. However, little is known about even the most widely distributed of these concerning the nature of the allergenic components of the spores. In 1939, Harris (Ref. 68) studied sera from 13 patients allergic to grain dusts and smuts using the passive transfer technique. Exhaustion of passively sensitized sites with *Alternaria* and *Hormodendrum* did not prevent subsequent strong reactions to wheat and oat dust. However, there was evidence of shared antigenicity between wheat and oat dust. On the other hand, cross-testing between different species of smut and rust indicated that there was some cross-neutralization; but the various species did show some differences. There was a close antigenic relationship between wheat dust and wheat smut.

Recommendations for Basidiomycetes extracts. Extracts of specifically identified individual *Basidiomycetes* should be placed in Category IIIA for both skin test diagnosis and immunotherapy.

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D. Miscellaneous Inhalant Allergenic Extracts

1. *Introduction.* Under normal conditions, the air we breathe always contains a variety of organic particles that are difficult to classify other than as miscellaneous. Some of these will be allergenic for some people and at times will be in adequate concentation to sensitize and, on reexposure, cause allergenic symptoms. Most of these substances play a minor role in production of allergenic symptoms in the general population but to certain individuals are quite important for one reason or another, frequently because of occupational exposure. Furthermore, it is likely that from time to time in the future, as has been true in the past, new substances will be discovered to be causes of allergic symptoms. Therefore, although the volume of demand for many of these products may not be great, provision should be made so that extracts of this type are available for diagnosis of therapy where a need in demonstrable.

Certain criteria should be expected for an extract of a substance responsible for inhalant allergic disease:

a. The extracted substance must be know to be present in the environment in a concentration sufficient to be expected to constitute an adequate exposure for individuals having symptoms.

b. There should be a history of patients having allergic symptoms occurring reasonably soon after exposure to the substance.

c. The extracted substance should be expected to contain material capable of being allergenic.

d. The substance should not be a primary irritant in the concentration which elicits allergic symptoms.

e. The extract should be capable of producing an allergic response on skin

testing an individual known to have allergic symptoms on exposure to the substance, or the extract should give a positive *in vivo* or *in vitro* test reacting with a patient's serum. In other words, it should show evidence of specific allergenicity.

f. The extract should be shown to be nontoxic in the dose range which will elicit allergic reactions.

g. The extract should not cause whealing reactions on nonallergic individuals in concentrations used for skin testing.

Table I lists miscellaneous inhalant extracts taken from the data submissions by manufacturers of extracts (Ref. 1). It is evident that some of the substances are made from variable sources such as grain dust, cotton linters, etc. In spite of this, if properly collected, many of these materials will have a distinctive allergenic character and the extracts of the substance have some degree of consistency from batch-to-batch.

The Panel followed the same principles used for reviewing pollens and other extracts. In general, if substantial data could be found to show that an extract was allergenic for skin test diagnosis but inadequate evidence for immunotherapy, it was placed in Category I for diagnosis and usually in Category IIIA for immunotherapy (Table II). If the extract was unproven in allergenicity (no data found) but the raw material was from an organic source likely to be allergenic, the extact was placed in Category IIIA for diagnosis and usually also for immunotherapy (Table III). An extract made from a raw material considered to be biochemically inert was placed in Category IIIB (Table IV). Extracts made from ill-defined source material, which would result in products with unpredictable allergenicity or toxicity, were also recommended for Category IIIB (Table V). If there are variations from this schema, they will be explained as each individual extract is discussed.

TABLE I.—MISCELLANEOUS INHALANT ALLERGENIC EXTRACTS

Extract	Evidence of allergenicity found by panel	Category recommendations	
		Skin test diagnosis	Immuno therapy
Algae	Yes	I	IIIA
Almond Hulls	No	IIIA	IIIA
Animal Feed Mix	No	IIIB	IIIB
Balsam Sawdust	No	IIIB	IIIB
Binder Twine	No	IIIB	IIIB
Castor Bean	Yes	I	IIIA
Cattail	No	IIIB	IIIB
Calk	No	IIIB	IIIB
Chicle	Yes	IIIA	IIIA
Chicory	No	IIIA	IIIA
Cleaning Tissue	No	IIIB	IIIB
Coconut Fiber	No	IIIA	IIIA

TABLE I.—MISCELLANEOUS INHALANT ALLERGENIC EXTRACTS—Continued

Extract	Evidence of allergenicity found by panel	Category recommendations	
		Skin test diagnosis	Immuno therapy
Cotton	No	IIIA	IIIA
Cotton, Aged	No	IIIA	IIIA
Cotton Gin Dust	No	IIIA	IIIA
Cotton Linters	Yes	I	IIIA
Cottonseed	Yes	I	IIIB
Dacron	No	IIIB	IIIB
Derris Root	Yes	IIIA	IIIB
Dust, Alfalfa Hay	No	IIIB	IIIB
Dust, Alfalfa Mill	No	IIIB	IIIB
Dust, Auto Upholstery.	No	IIIB	IIIB
Dust, Barley	No	IIIB	IIIB
Dust, Barn	No	IIIB	IIIB
Dust, Brome Corn	No	IIIB	IIIB
Dust, Chicken House	No	IIIB	IIIB
Dust, Clover Hay	No	IIIB	IIIB
Dust, Combined	No	IIIB	IIIB
Dust, Grain Elevator	No	IIIB	IIIB
Dust, Grain Elevator (Grain Mill Dust or Grain Dust Mix).	Yes	IIIA	IIIA
Dust, Furniture Upholstery.	No	IIIB	IIIB
Dust, Hay	No	IIIB	IIIB
Dust, Prairie Hay	No	IIIB	IIIB
Dust, Kafir	No	IIIB	IIIB
Dust, Lespedeza Hay.	No	IIIB	IIIB
Dust, Milo	No	IIIB	IIIB
Dust, Oat	No	IIIB	IIIB
Dust, Pea	No	IIIB	IIIB
Dust, Pencil	No	IIIB	IIIB
Dust, Poultry	No	IIIB	IIIB
Dust, Rice	No	IIIB	IIIB
Dust, Road	No	IIIB	IIIB
Dust, Rye	No	IIIB	IIIB
Dust, Soy Bean	No	IIIB	IIIB
Dust, Timothy Hay	No	IIIB	IIIB
Dust, Wheat	No	IIIB	IIIB
Excelsior	No	IIIB	IIIB
Fern Spores	No	IIIA	IIIA
Fiber Glass	No	IIIB	IIIB
Flax Fiber	No	IIIA	IIIA
Flaxseed	Yes	I	IIIB
Glue	No	IIIB	IIIB
Glue, Animal	No	IIIB	IIIB
Glue, Fish	Yes	IIIB	IIIB
Glue, Liquid	No	IIIB	IIIB
Glue, Powdered	No	IIIB	IIIB
Gum Guar	Yes	IIIA	IIIA
Gum Arabic or Acacia.	Yes	I	IIIA
Gum Carbo	No	IIIA	IIIA
Gum India (Karaya)	Yes	I	IIIA
Gum Tragacanth	Yes	I	IIIA
Hemp Dust	No	IIIA	IIIA
Ipecac	Yes	IIIA	IIIA
Jute	No	IIIA	IIIA
Kapok	Yes	IIIA	IIIA
Lampblack	No	IIIB	IIIB
Lavender	No	IIIA	IIIA
Linen	No	IIIB	IIIB
Lycopodium	No	IIIA	IIIA
Malt	No	IIIA	IIIA
Monsanto Enzyme (B. Subtilis, Novoenzyme.	Yes	I	IIIA
Newspaper	No	IIIB	IIIB
Newspaper Mix (Printed).	No	IIIB	IIIB
Newspaper/ Newspaper Print.	No	IIIB	IIIB
Nylon	No	IIIB	IIIB
Orris Root	Yes	IIIA	IIIA
Paper, Carbon	No	IIIB	IIIB
Paper, Mix	No	IIIB	IIIB
Paper, Pulp	No	IIIB	IIIB
Psyllium Seed	No	IIIA	IIIA
Pyrethrum	Yes	IIIA	IIIA
Rapeseed	No	IIIA	IIIA
Rayon	No	IIIB	IIIB
Rose Spp.	No	IIIA	IIIA
Rug	No	IIIB	IIIB
Sea Moss	No	IIIA	IIIA
Senna	No	IIIA	IIIA
Silk	Yes	I	IIIA
Sisal	No	IIIA	IIIA

TABLE I.—MISCELLANEOUS INHALANT ALLERGENIC EXTRACTS—Continued

Extract	Evidence of allergenicity found by panel	Category recommendations	
		Skin test diagnosis	Immuno therapy
Smoke, Cigar	No	IIIB	IIIB
Smoke, Cigarette	No	IIIB	IIIB
Smoke, Tobacco	No	IIIB	IIIB
Tobacco Smoke-Mixture.	No	IIIB	IIIB
Snuff, Mix	No	IIIB	IIIB
Spanish Moss	No	IIIB	IIIB
Tobacco Leaf, green	Yes	I	IIIA
Tobacco Leaf, cured	Yes	IIIA	IIIA
Tobacco, Cigar	Yes	IIIB	IIIB
Tobacco, Cigarette	Yes	IIIB	IIIB
Tobacco, Mix	Yes	IIIB	IIIB
Tobacco, Pipe	Yes	IIIB	IIIB
Wood dusts:			
Busal	No	IIIA	IIIA
Beech	No	IIIA	IIIA
Birch	No	IIIA	IIIA
Cedar and Red Cedar.	Yes	I	IIIA
Cocabola	Yes	I	IIIA
Cottonwood	No	IIIA	IIIA
Elm	No	IIIA	IIIA
Fir	No	IIIA	IIIA
Fir, Douglas	No	IIIA	IIIA
Fir, Red	No	IIIA	IIIA
Fir, White	No	IIIA	IIIA
Helmlock	No	IIIA	IIIA
Mahogany	No	IIIA	IIIA
Maple	No	IIIA	IIIA
Oak, Red	Yes	I	IIIA
Oak, White	Yes	I	IIIA
Padauk	Yes	I	IIIA
Pine, White	No	IIIA	IIIA
Pine, Yellow	No	IIIA	IIIA
Redwood	No	IIIA	IIIA
Spruce	No	IIIA	IIIA
Tamarack (Larch)	No	IIIA	IIIA
Walnut	No	IIIA	IIIA

TABLE II.—ALLERGENIC EXTRACTS OF MISCELLANEOUS SUBSTANCES WITH DATA OF ALLERGENICITY FOUND

Category recommendations	Extract	
	Skin test diagnosis	Immuno therapy
Algae	I	IIIA
Castor Bean	I	IIIA
Cotton Linters	I	IIIA
Cottonseed	I	IIIB
Flax Seed	I	IIIB
Gum Arabic or Acacia	I	IIIA
Gum India (Karaya)	I	IIIA
Gum Tragacanth	I	IIIA
Bacillis Subtilis Enzyme (Monsanto enzyme, Novoenzyme).	I	IIIA
Silk	I	IIIA
Cedar Wood Dust	I	IIIA
Cocabola Wood Dust	I	IIIA
Oak Wood Dust (Red and White Oak).	I	IIIA
Padauk Wood Dust	I	IIIA
Tobacco Leaf, green	I	IIIA

TABLE III.—ALLERGENIC EXTRACTS OF MISCELLANEOUS DEFINED ORGANIC SUBSTANCES LIKELY TO BE ALLERGENIC

Extract	Category recommendations	
	Skin test diagnosis	Immunotherapy
Almond Hulls	IIIA	IIIA
Chicle	IIIA	IIIA
Chicory	IIIA	IIIA
Coconut Fiber	IIIA	IIIA
Cotton	IIIA	IIIA
Cotton, aged	IIIA	IIIA

TABLE III.—ALLERGENIC EXTRACTS OF MISCELLANEOUS DEFINED ORGANIC SUBSTANCES LIKELY TO BE ALLERGENIC—Continued

Extract	Category recommendations	
	Skin test diagnosis	Immunotherapy
Cotton Gin Dust	IIIA	IIIA
Derris Root	IIIA	IIIB
Fern Spores	IIIA	IIIA
Flax Fiber	IIIA	IIIA
Gum Guar	IIIA	IIIA
Gum Carbo	IIIA	IIIA
Hemp Dust	IIIA	IIIA
Ipecac	IIIA	IIIA
Jute	IIIA	IIIA
Kapok	IIIA	IIIA
Lavender	IIIA	IIIA
Lycopodium	IIIA	IIIA
Orris Root	IIIA	IIIA
Malt	IIIA	IIIA
Psyllium Seed	IIIA	IIIA
Pyrethrum	IIIA	IIIA
Rapeseed	IIIA	IIIA
Rose spp	IIIA	IIIA
Sea Moss	IIIA	IIIA
Senna	IIIA	IIIA
Sisal	IIIA	IIIA
Spanish Moss	IIIB	IIIB
Tobacco Leaf, cured	IIIA	IIIA
Wood Dusts:		
Busal	IIIA	IIIA
Beech	IIIA	IIIA
Birch	IIIA	IIIA
Cottonwood	IIIA	IIIA
Elm	IIIA	IIIA
Fir	IIIA	IIIA
Fir, Douglas	IIIA	IIIA
Fir, Red	IIIA	IIIA
Fir, White	IIIA	IIIA
Hemlock	IIIA	IIIA
Mahogany	IIIA	IIIA
Maple	IIIA	IIIA
Pine, White	IIIA	IIIA
Pine, Yellow	IIIA	IIIA
Redwood	IIIA	IIIA
Spruce	IIIA	IIIA
Tamarack (Larch)	IIIA	IIIA
Walnut	IIIA	IIIA

TABLE IV.—EXTRACTS OF MISCELLANEOUS SUBSTANCES CONSIDERED TO BE BIOCHEMICALLY INERT

Extract	Category recommendations	
	Skin test diagnosis	Immunotherapy
Dacron	IIIB	IIIB
Fiberglass	IIIB	IIIB
Nylon	IIIB	IIIB
Rayon	IIIB	IIIB

TABLE V.—ALLERGENIC EXTRACTS OF POORLY DEFINED SUBSTANCES

Extract	Category recommendations	
	Skin test diagnosis	Immunotherapy
Animal Feed Mix	IIIB	IIIB
Balsam Sawdust	IIIB	IIIB
Binder Twine	IIIB	IIIB
Cattail	IIIB	IIIB
Chalk	IIIB	IIIB
Cleansing Tissue	IIIB	IIIB
Dust, Alfalfa Hay	IIIB	IIIB
Dust, Alfalfa Mill	IIIB	IIIB
Dust, Auto Upholstery	IIIB	IIIB
Dust, Barley	IIIB	IIIB
Dust, Barn	IIIB	IIIB
Dust, Brome Corn	IIIB	IIIB
Dust, Chicken House	IIIB	IIIB
Dust, Clover Hay	IIIB	IIIB

TABLE V.—ALLERGENIC EXTRACTS OF POORLY DEFINED SUBSTANCES—Continued

Extract	Category recommendations	
	Skin test diagnosis	Immunotherapy
Dust, Combined	IIIB	IIIB
Dust, Elevator (Grain Elevator dust, Grain mill dust or Grain dust mix).	IIIA	IIIA
Dust, Furniture Upholstery	IIIB	IIIB
Dust, Hay	IIIB	IIIB
Dust, Prairie Hay	IIIB	IIIB
Dust, Kafir	IIIB	IIIB
Dust, Lespedeza Hay	IIIB	IIIB
Dust, Milo	IIIB	IIIB
Dust, Oat	IIIB	IIIB
Dust, Pea	IIIB	IIIB
Dust, Pencil	IIIB	IIIB
Dust, Poultry	IIIB	IIIB
Dust, Rice	IIIB	IIIB
Dust, Road	IIIB	IIIB
Dust, Rye	IIIB	IIIB
Dust, Soybean	IIIB	IIIB
Dust, Timothy Hay	IIIB	IIIB
Dust, Wheat	IIIB	IIIB
Excelsior	IIIB	IIIB
Glue	IIIB	IIIB
Glue, Animal	IIIB	IIIB
Glue, Fish	IIIB	IIIB
Glue, Liquid	IIIB	IIIB
Glue, Powdered	IIIB	IIIB
Lampblack	IIIB	IIIB
Linen	IIIB	IIIB
Newspaper	IIIB	IIIB
Newspaper Mix (Printed)	IIIB	IIIB
Newspaper/Newspaper Print	IIIB	IIIB
Paper, Carbon	IIIB	IIIB
Paper Mix	IIIB	IIIB
Paper Pulp	IIIB	IIIB
Rug	IIIB	IIIB
Smoke, Cigar	IIIB	IIIB
Smoke, Cigarette	IIIB	IIIB
Smoke, Tobacco	IIIB	IIIB
Smoke, Tobacco Mixture	IIIB	IIIB
Snuff Mix	IIIB	IIIB
Tobacco, Cigar	IIIB	IIIB
Tobacco, Cigarette	IIIB	IIIB
Tobacco Mix	IIIB	IIIB
Tobacco, Pipe	IIIB	IIIB

2. *Algae: Subkingdom—Thallophyta*—a. *Introduction.* Algae grow in almost every region of the world. Most of them live on water, some grow on plants, and some on animals. All algae contain chlorophyll. Many species are mobile, others that cannot move produce motile reproductive cells called gametes or spores. Aerial distribution is possible and although data are incomplete, there is evidence to show that algal spores can be detected in sufficient quantity to be considered symptom producing levels (Ref. 2).

There are four main classes: Blue-green Algae, *Cyanophyta;* Green Algae, *Chlorophyta;* Brown Algae, *Phaeophyta;* and Red Algae, *Rhodophyta.*

Of 79 atopic patients tested in a study by Bernstein et al., 47 exhibited positive skin reactions of two plus or greater to one or more of six algal antigens tested. The species of algae were *Chlorella pyrenoidosa, Scenedismus basilensis, Chlorococcum botryoides, Ankistrodesmus falcatus, Chlorella vulgaris* and *Chlorococcum macrostigmatum.* Nonallergic patients showed no skin reactivity to these antigens. Skin sensitizing antibodies were passively transferred from six of eight patients tested with *Chlorella vulgaris.* Positive bronchial challenge was obtained in five of these patients (Ref. 2).

Patients with symptoms of perennial allergic rhinitis also have a high incidence of skin reactivity to various green algae, particularly to a *Chlorella* species isolated from unprocessed house dust (Ref. 3) and some dust samples have shown significant amounts of algal spores.

b. *Manufacturing.* In one technique (Ref. 2), algal cells are cultured in media, harvested by centrifugation, washed with distilled water and extracted in Coca's solution. The cells may be ruptured by treating for 30 minutes in an ultrasonic disintegrator. The suspension is then centrifuged, and the supernatant passed through a sterilizing filter.

c. *Antigenic relationships.* Knowledge concerning cross reactivity between various species of algae is incomplete. It would appear that there may be very little shared antigenicity between species since many of the patients reacted to only one species (Ref. 2). There is also evidence that algae may contribute to some degree to the allergenicity of some lots of house dust (Ref. 3).

d. *Effectiveness for skin test diagnosis.* The Panel has found one reported study (Ref. 3) which states that:

Although skin test allergenicity to green algae was confirmed by passive transfer and bronchial provocation test, cutaneous reactivity was not necessarily pathognomonic of clinical sensitivity * * * it should be emphasized that positive nasal and LHR (leucocyte histamine release) responses were obtained only in patients with skin test reactivity greater than 3+. Thus, skin testing, though somewhat limited in specificity, will nevertheless continue to serve as a useful diagnostic aid in the initial evaluation of algae hypersensitivity.

e. *Effectiveness for immunotherapy.* The Panel has found no controlled studies indicating that algae extracts will reduce symptoms of algae sensitivity better than placebo or will induce changes in algae-specific IgG or IgE antibodies.

f. *Critique.* The reported studies with algae establish that it does cause allergic sensitization and will produce symptoms of hay fever and asthma in sensitized individuals upon controlled exposure. Within the limits inherent to the technique, extracts of algae are useful as skin test agents in diagnosing clinical sensitivity to algae. The Panel

has found no evidence that these extracts are useful in immunotherapy, but concludes by analogy that, like other substances which show immunological activity, algae extracts could reasonably be expected to have effectiveness in treatment of allergic disorders caused by exposure to algae.

g. *Recommendations.* It is recommended that algae extracts with the species identified be placed in Category I for skin test diagnosis and in Category IIIA for immunotherapy.

3. *Almond hulls.* The Panel has not seen documented evidence of inhalant allergenicity to almond (*Prunus amygdalus*) hulls. The source material is judged to be capable of causing allergic sensitization based upon its organic proteinaceous nature. It is recommended that extract of almond hulls be placed in Category IIIA for both skin test diagnosis and immunotherapy.

4. *Animal feed mix.* The Panel has not seen documented evidence of allergenicity of animal feed mix. The source material is judged to be capable of causing allergic sensitization, but animal feeds are prepared products of variable nature, and the source materials would not be uniform. It is recommended that extracts of animal feed mix be placed in Category IIIB.

5. *Balsam sawdust.* The Panel has not seen documented evidence of allergenicity of balsam sawdust and the source material is not defined as to whether it refers to sawdust of balsa (*Ochroma pyramidale*) or to the resinous substances "balsam" present in many woods. It is recommended that extracts of balsam sawdust be placed in Category IIIB.

6. *Binder twine.* Allegenicity of binder twines is not documented. These are manufactured products and the source materials would not be uniform. It is recommended that extracts of binder twine be placed in Category IIIB.

7. *Castor bean*—a. *Introduction.* A number of cases of inhalant sensitization to castor bean (*Ricinus communis*) dust have been reported by several authors (Refs. 4 through 7). Persons most likely to incur exposure are workers handling castor beans or handling sacks which formerly contained castor beans. Castor bean dust is an extremely potent sensitizer, and a small amount of exposure will produce extremely severe symptoms in sensitive individuals. Likewise, testing with castor bean extracts has shown that very dilute solutions produce diagnostically significant reactions (Ref. 6).

Coulson, et al. (Ref. 8) reported on fractions of crude bean antigen and identified a highly antigenic (for guinea pigs) anaphylactic fraction which they called CB–1A. This fraction had a relatively small molecular weight, was dialyzable, was quite similar in molecular structure to a cottonseed fraction, and consisted of protein as well as polysaccharide components. The authors felt that the carbohydrate moiety of CB–1A did not influence antigenic specificity but did enhance the sensitizing capacity of the protein component.

b. *Manufacturing.* Castor bean dust contains ricin which is toxic (Refs. 6 and 7) and which must be removed in the extracting process. Barnard (Ref. 6) showed the active principle to be soluble in water, precipitated by alcohol, heat stable (resists boiling) and not dialyzable. As noted above, Coulson's anaphylactic fraction was dialyzable and was probably more purified.

c. *Effectiveness for skin test diagnosis.* The Panel found published papers indicating that extracts of castor bean dust are effective in diagnosing allergy caused by exposure to castor bean dust (Refs. 4 through 7).

d. *Effectiveness for immunotherapy.* Castor bean dust extract is highly potent, and if used in immunotherapy, it would entail a high risk to benefit ratio. Furthermore, avoidance of the substance would seem to be the most practical therapy in most instances.

e. *Critique.* Castor bean has been shown to cause allergic sensitization, and the extract, properly diluted, gives diagnostically significant skin reactions. The extract is biologically active and by analogy to other alergenic extracts would presumably produce favorable immunological responses if used in immunotherapy, but has not been demonstrated in adequate and well-controlled studies. The Panel feels that the risk-to-benefit ration for use in immunotherapy is high, and that avoidance of exposure should be possible in the great majority of instances.

f. *Recommendation.* It is recommended that extract of castor bean be placed in Category I for skin test diagnosis and in Category IIIA for immunotherapy.

8. *Cattail.* Cattail. *(Typha latifolia* or *angustifolia)* is listed under "Miscellaneous Extracts" by a manufacturer but the firm did not specifiy what part of the cattail, i.e., pollen, seed, etc. is used as the source material. Based upon the lack of definition of the source material and its realtionship to allergic disease, it is recommended that cattail extracts be placed in Category IIIB.

9. *Chalk.* Pure chalk consists largely of fossilized shells of tiny prehistoric sea animals and crystals of calcite. It is therefore judged to be not allergenic. Blackboard chalk is manufactured using gums or adhesives to hold the chalk together. It is a variable product and the source lacks definition. It is recommended that chalk extracts be placed in Category IIIB.

10. *Chicle.* Chicle is a product derived from the sap of the sapodilla tree *(Achras sapota).* It was at one time an important ingredient of chewing gum but has now been largely replaced by synthetic material. Vaughn and Black (Ref. 9) cite Kleinman, who reported two cases of allergy to chicle; but only one of these responded with positive skin test (which progressed to a systemic reaction) and to mucous membrane challenge by chewing gum. Control tests in 25 other allergic patients and 6 nonallergic persons were negative, except for one moderately positive test, but with no confirmatory clinical history.

There is information on only one reported case in 1935 and no indication that chicle is an allergen of any serious consequence. There is widespread use of chewing gum and nothing to suggest that it is even a rare cause of clinical symptoms. It is recommended that extracts of chicle be placed in Category IIIA for both skin test diagnosis and immunotherapy.

11. *Chicory.* Chicory *(Chichorium intybus)* is a small plant whose leaves are used as salads, the young roots can be used as a cooked vegetable and mature roots are roasted and mixed with coffee. There is no information concerning its allergenicity, although it is a member of the *Compositae* family and could conceivably share antigenicity with other *Compositae* members. It is recommended that chicory extracts be placed in Category IIIA for both skin test diagnosis and immunotherapy.

12. *Cleansing tissue.* Since this is a manufactured product, the source material is not constant and lacks definition. It is recommended that cleaning tissue extracts be placed in Category IIIB.

13. *Coconut fiber.* The husk of the coconut *(Cocos nucifera)* yields short stiff fibers called *coir,* which are made into ropes, doormats, and brooms. There are no data to show that coconut fiber is an allergen. However, the raw material is from an organic source likely to be allergenic. The Panel recommends that extracts of coconut fiber be placed in Category IIIA for both skin test diagnosis and immunotherapy.

14. *Cotton, aged cotton and cotton gin dust (Gossypium spp.).* Cotton, aged cotton and cotton gin dust are discussed together, since all are derived from the same organic source. Aged cotton and cotton gin dust both contain fibers which are too short for making textiles. There may be a difference in that aged cotton presumably once consisted of longer fibers; but as a result of degenerative processes such as oxidation, digestion by microorganisms, action of enzymes, etc. over a period of time, the fibers have been broken down and a residue of dust results. On the other hand, cotton gin dust is mechanically produced by cutting short fibers of cotton which are adherent to the seed. Cotton gin dust has been studied more extensively than dust of aged cotton, since it is an important industrial hazard.

Dust in cotton mills is an industrial air pollutant which has been found to cause a specific chronic lung disease called byssinosis (Ref. 10). A sufficient number of studies has been done to establish the fact that byssinosis is not likely to be dependent upon allergic mechanisms, but is probably due to the fact that cotton dust either contains substances capable of inducing histamine release from normal, i.e., nonallergic, lung tissue (Refs. 11 through 13) or has an endotoxin like action from the bacterial contamination of the cotton. An early textbook (Ref. 14) reported cotton fiber to be allergenic; however, there is very little evidence in subsequent literature to support this statement. By analogy, the disease byssinosis would be somewhat related to "grain fever" caused by exposure to excessive amounts of grain dust. Whereas, allergic symptoms to either grain dust or cotton dust would be caused by minimal exposure. Byssinosis is an important industrial disease and consequently has received more attention than cotton dust allergy. The evidence for cotton dust as an allergen for humans is lacking. Experimentally, it has been shown that cotton dust derived from bract will produce specific rabbit antibodies; but whether this related to human allergy is not known (Ref. 15).

Cotton is related to kapok botanically; however, there is little evidence concerning allergic cross-sensitivity.

There is no information about cotton extracts effectiveness for skin test diagnosis or for immunotherapy.

Although its histamine releasing properties overshadow its potential allergenic properties, cotton dust is an organic substance with potential for allergenicity.

The Panel recommends that extracts of cotton and cotton gin dust be placed in Category IIIA for both skin test diagnosis and immunotherapy.

15. *Cotton linters.* The linters of cotton *(Gossypium hirsutum),* or the short fuzz which remains on the seed after the long fiber has been removed, is used as raw material for products in which cellulose is a base, such as guncotton, photographic film, paper, and rayon; and it is also used as stuffing in mattresses and furniture. The history of cotton linters as an allergen is connected with the efforts to identify the allergens of house dust. Cohen (Ref. 16) and Cazort (Ref. 17) presented evidence to show that aged cotton linters were allergenic and cross-reacted on patients allergic to house dust. Boatner and Efron (Ref. 18) described a method of preparing a concentrate of house dust in which cotton mattress dust was used as the starting material.

Coulson and Stevens (Ref. 19) found common antigens in cotton linters and house dust which could produce anaphylaxis in the guinea pig. However, this finding may not have meaning in human allergy since other authors (Refs. 20 through 22) have shown that components of allergenic extracts which induce antibody formation in animals are not the same components which are the major causes of allergy in man.

Regardless of the relationship of cotton linters to house dust, studies have shown that extracts of cotton linters are allergenic for man as evidence by direct skin tests and by passive transfer. Furthermore, heavy exposure to cotton linters such as is experienced by workers in the cotton industry is not necessary for an individual to develop allergic sensitization. These observation establish cotton linters as a ubiquitous allergen for man. Cotton linters are also linked to house dust either as a component itself or perhaps as a substrate for a component as suggested by Berrens (Ref. 23).

Coulson and Stevens (Ref. 19) point out that cotton linters are available in a number of different grades based on the amount of contaminating plant particles such as stem, leaf and seed hull and also on the color of the fiber influenced by weathering in the field or by action of microorganisms. They conclude that it is difficult to obtain a sample of linters that would be representative of all linters. Follensby, et al. (Ref. 22), in testing the original idea of Cohen (Ref. 16) and Cazort (Ref. 17) that aged linters are allergenic while fresh linters are not, agreed that this was true.

Coulson and Stevens (Ref. 19) also identified a nonspecific toxic substance in linters extract which would produce anaphylactic like symptoms when injected intravenously into guinea pigs. They found this substance to be present in dialyzed extracts, as well as in the dialyzate. Accordingly to Hampton and Stull (Ref. 24), however, dialyzing the extract removed the toxic activity and Evans and Nicholls (Ref. 25) have demonstrated that cotton dust extracts will release histamine in human lung. In earlier experiments, the histamine releasing substance was shown (Ref. 26) to be dialyzable.

Attempts to demonstrate shared antigenicity of cotton linters with other allergens such as kapok, hay, and human and animal dander with respect to the components important to human allergy have not been successful (Refs. 19, 22, 23, and 27).

There is evidence of allergenicity of cotton linters extract, as mentioned above. Wagner and Rackemann (Ref. 27) found that extracts of old cotton linters yielded an incidence of 64 percent positive direct skin tests in 80 allergic patients and 50 percent in 30 normal controls. However, 15 percent of the allergic patients had demonstrable reagins and none of the controls had reagins. The high number of positive reactions among the controls and some of the reactions in the allergic patients may have been due to the concentration as well as the impurity of the extract used.

No data are available for extracts of cotton linters effectiveness for immunotherapy except as a component of house dust and Endo Dust which are discussed later in this document.

From the earliest references to those of recent years, the accumulated evidence is that cotton linters are allergenic for man. There is evidently widespread human exposure to dust from cotton linters apart from the industrial exposure discussed in the previous section on cotton, aged and cotton gin dust. The Panel advises that cotton linters are an important source of allergic sensitization in many homes as well as in industry, and it is desirable that extracts of cotton linters be available.

The Panel recommends that extract of cotton linters be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy. The source of raw material for cotton linters extract should adhere as closely as possible to uniform specifications as to grade and age. Dialysis or some suitable means of removing histamine liberating substances should be an essential manufacturing step.

16. *Cottonseed.* Cottonseed (*Gossypium* spp.) is an important allergen but only for a few individuals. It

is chiefly encountered in food in the form of cottonseed meal which is used in bakery goods and, in this form, it has been known to produce violent allergic reactions. On the other hand, cottonseed oil as it is prepared today contains little or no protein residue and is of questionable allergenicity.

Because of the extreme potency of cottonseed extracts, the material needs to be diluted properly prior to testing. Early in the history of the specialty of allergy, several deaths from intradermal testing with cottonseed allergen were reported (Refs. 28 through 30). As a result, it has been the common practice to limit the use of the cottonseed allergen for cutaneous testing only.

Cottonseed extract is an organic substance generally recognized in standard medical texts as an effective agent in confirming diagnosis of allergy to cottonseed.

Since avoidance of cottonseed is usually possible, immunotherapy with cottonseed extract is usually unnecessary and may be the reason for the lack of published evidence of effectiveness. In certain instances, cottonseed extract is valuable as a means of confirming diagnosis to cottonseed allergy.

The Panel recommends that extract of cottonseed be placed in Category I for skin test diagnosis. In addition, the labeling should include a warning that cottonseed extract is an extremely potent allergen and it should not be recommended for intradermal testing without proper dilution. Cottonseed extracts should be placed in Category IIIB for immunotherapy because of the risk of unexpected reactivity whether due to the unknown potency of the extracts or due to variations in individual patient sensitivity.

17. *Dacron.* Dacron is a synthetic fiber polymer derived from coal, air, water, petroleum, limestone and natural gases. This material is generally recognized to be biochemically inert and is judged to be incapable of causing allergic responses. The Panel recommends that extract of dacron be placed in Category IIIB.

18. *Derris root.* Derris root (*Lonchocarpus species*) is a genus of tropical shrubs embracing about 40 species. Rotenone has been isolated as one of the most potent active principles of derris for use as an insecticide. Derris root is not as widely used as an insecticide as it once was and has lost some relevancy as an industrial or household hazard.

Weston (Ref. 31) reported two cases of bronchial asthma due to exposure to flea powder containing derris root. An extract of the powder was made by defatting with anhydrous ether, extracting with Coca's fluid for 24 hours, filtering, dialyzing, and finally sterilizing by Seitz filtration. The resulting extract was found to contain 0.4 mg of nitrogen per cc. Dilutions of 0.0001, 0.001, and 0.01 mg of nitrogen per cc were used for intradermal testing. One case reacted strongly to 0.01 mg/mL strength and the other to 0.001 mg/mL. Neither case reacted to pyrethrum, another plant powder with insecticidal properties. Passive transfer tests were not done. Defatting and dialysis may be necessary manufacturing steps.

The data mentioned previously show that derris root extract will detect skin sensitivity in individuals with allergic symptoms due to exposure to derris root powder. There were no data on testing normal controls nor were passive transfer or RAST done.

Immunotherapy should not be necessary for derris root since avoidance of exposure should be possible. Furthermore, there is not sufficient evidence concerning human toxicity to rotenone to consider derris root extract safe for repeated injection in human subjects.

With the development of potent synthetic insecticides, products such as derris root are less in evidence and human exposure is not frequent. However, naturally occurring insecticides may regain popularity if industrial processes become more expensive or are found to have increasingly undesirable effects in contaminating air or water supplies. Therefore, derris root should probably not be totally disregarded as a potential allergen; although it does not appear to be an important cause of allergic symptoms at this time. The Panel recommends that extracts of derris root be placed in Category IIIA for skin test diagnosis and Category IIIB (because of the potential safety hazard) for immunotherapy.

19. *Dust, alfalfa hay.* No mention of extracts of dust from alfalfa hay (*Medicago sativa*) could be found in the literature. It is likely that dust from dried alfalfa could trigger allergic symptoms. Such dust would be expected to consist of fine particles derived from the alfalfa plant, mold spores, basidiomycetes spores, and bacteria, plus minor contaminants such as insect parts, products of animal origin, pollen, etc. Alfalfa hay dust may well have characteristics that would distinguish it from other farm dusts, but this is not known. It is reasonable to assume that some of its allergenic characteristics are due to contaminants other than the material derived from the alfalfa plant itself.

Because of bacterial contamination, alfalfa hay dust would be expected to have a high endotoxin content.

Alfalfa hay dust has an organic source and has potential as an allergen. It is probably impossible to separate alfalfa hay dust from other potential allergens. The Panel recommends that extracts of alfalfa hay dust be placed in Category IIIB.

20. *Dust, alfalfa mill.* The comments for "Dust, alfalfa hay (*Medicago sativa*)" apply similarly to alfalfa mill dust. It is worth commenting, however, that alfalfa dehydrating plants have a particularly offensive odor that can be detected for considerable distances. Presumably, the odor could act as a chemical irritant in exciting allergic symptoms. It is recommended that extracts of alfalfa mill dust be placed in Category IIIB.

21. *Dust, auto upholstery.* "Auto upholstery dust" is too indefinite as a description of the source of material for preparation of an allergenic extract. Unless the dust contains some extraordinary contaminant, it may be similar to house dust. The Panel believes that it is not possible to establish a consistent source of raw material for extraction and therefore recommends that automobile upholstery dusts be placed in Category IIIB.

22. *Dust, barley.* Like alfalfa hay dust, dust from barley (*Hordeum vulgare*) may have characteristics of its own that distinguish it from other dusts of vegetable origin, but nothing was found in the literature about barley dust. Barley is a source material with allergenic potential, but the dust may contain variable contaminants. The Panel recommends that barley dust extracts be placed in Category IIIB.

23. *Dust, barn.* The Panel believes that barn dust is likely to be a mixture of other better-defined substances and need not be retained as a specific allergen. It would be too difficult to define a safe source of raw material for extraction. The Panel recommends that barn dust extracts be placed in Category IIIB.

24. *Dust, brome corn.* The comments for "Dust, alfalfa hay" apply similarly to brome corn (Broom Corn, another variety of *Sorghum vulgare*) dust extracts. There is nothing in the literature with special reference to broom corn. Ninety percent of broom corn used in the United States is imported from Mexico and is already processed. Broom corn dust is no longer a widespread industrial problem. The Panel recommends that extracts of brome corn dust be placed in Category IIIB.

25. *Dust, chicken house.* The comments for "Dust, barn" apply similarly to chicken house dust extracts. The Panel recommends that extracts of chicken house dust extracts be placed in Category IIIB.

26. *Dust, clover hay.* Several clover varieties are cultivated, including red clover (*Trifolium pratense*), white clover (*Trifolium repens*), alsike (*Trifolium hybridum*), crimson clover (*Trifolium incaratum* white sweet clover (*Melilotus alba*), yellow sweet clover (*Melilotus officianalis*), and sour clover (*Melilotus indica*). The *Trifolium* species are probably closely botanically related, but are different from the *Melilotus* species. The comments for "Dust, alfalfa hay" apply similarly to clover hay dust extracts. There is nothing in the literature with special reference to dust from clover hay. If there should prove to be something unique about clover hay as an allergen, the species should be identified and the extract prepared in a way to exclude potential contaminants. It is recommended that clover hay dust extracts be placed in Category IIIB.

27. *Dust, combined.* "Dust combined" is too indefinite as a description of the source of material for extraction and would be expected to contain a mixture of allergens obtainable from more clearly defined sources. It is recommended that combined dust extracts be placed in Category IIIB.

28. *Dust, grain elevator, grain dust or elevator dust*—a. *Introduction.* "Grain elevator dust", "grain dust", "grain mill dust", or "elevator dust" are not well-defined substances, but are presumed to be a collection of light-weight organic particles which rub off grain (wheat, corn, oats, milo, etc.) during movement of the grain in storage facilities, plus a mixture of many other substances. Such materials will accumulate on rafters and can be gathered by brushing the material off the rafters into a bag.

Persons in neighborhoods located as much as a mile downwind from grain storage elevators are known to have sufficient exposure to grain dust to develop allergic sensitization and symptoms (Ref. 32). Grain dust is also an occupational hazard for grain handlers who at times may be exposed to heavy concentrations. Two types of symptoms may occur as a result of exposure to grain dust:

(1) A syndrome; "grain fever" which consists of malaise, myalgia, headache, leucocytosis and chills and fever, may occur in nonallergic as well as allergic subjects. This syndrome appears to be similar to that associated with other organic dusts such as byssinosis which is caused by cotton gin dust. The mechanism involved is not thought to be immunologic and requires exposure to a heavy concentration of dust.

(2) Asthma (wheezing) is immunologically mediated and occurs in allergic subjects following exposure to small amounts of allergen (Ref. 32).

Grain dust is a mixture of a number of potential allergens including organic material derived not only from the grains of origin, but also may contain other substances, thermophilic bacteria, mites, insects, animal emanations (especially rodent dander, urine, or feces), molds, smuts and pollens, to name a few. In spite of this, patients with skin sensitivity to grain dust do not consistently react to any other allergen or allergens; although, no patient in the study referred to above reacted solely to grain dust (Ref. 32).

Harris (Ref. 33) studied sera from 13 patients who were allergic to grain dusts and smut. He used the passive transfer technique and found evidence of shared antigenicity between wheat and oat dust and between wheat smut and wheat dust. But until the allergens of grain dust are better characterized, there can only be speculation concerning allergenic components and shared allergenicity.

b. *Effectiveness for skin test diagnosis.* One study (Ref. 32) of 17 asthmatic workers showed that 8 of 17 gave a positive skin reaction of the immediate type to grain dust extract. After bronchial inhalation challenge with grain dust extract, 7 of the 8 developed respiratory symptoms. One additional patient with no skin hypersensitivity to grain dust extract had respiratory symptoms after bronchial challenge. The grain dust was prepared from samples collected from the subject's place of work. In the same study, commercial grain dust extract purchased from Hollister-Stier was used in skin testing and positive reactions occurred in 4 of the 8 subjects who reacted to the autogenous grain dust extracts. Of the 17 subjects with asthmatic symptom who were tested, 9 did not react to any of the grain dust extracts; and 12 nomal subjects also did not react. Therefore, grain dust extract is not likely to be a primary skin irritent.

As previously mentioned, Harris (Ref. 33) was able to demonstrate positive passive transfer in 13 patients allergic to grain dusts. RAST studies have not been reported.

c. *Effectiveness for immunotherapy.* The Panel found no adequate and well-controlled studies showing effectiveness of grain dust extract to be more useful in reducing symptoms due to exposure to grain dust than placebo. There were no reports showing favorable immunological responses of a result of treatment. Grain dust extract has been accepted by competent allergists as being effective in immunotherapy to reduce allergic symptoms due to exposure to gain dust by analogy to other immunologically active inhalant allergens, such as pollens and molds.

d. *Critique.* The greatest objection to considering grain dust as an allergenic entity is its variable nature depending upon its source of origin. Yet, Harris (Ref. 33) found evidence of shared antigenicity between wheat and oat dust; and there is sufficient evidence to show that grain dust is an allergen. On the other hand, in the series reported by Warren et al. (Ref. 32), autogenous grain dust appeared to be more accurately diagnostic than commercially obtained grain dust. In spite of these discrepancies, it would appear that grain dust has allergenic properties and its relationship in allergic disease is similar to the dilemma with house dust extracts and house dust allergy. Therefore, if properly collected and prepared, grain dust should be a useful allergen; although further study of its characteristics is still needed.

e. *Recommendation.* It is recommended that clearly identified elevator grain dust extracts be placed in Category IIIA for both skin test diagnosis and immunotherapy.

29. *Dust, furniture upholstery.* The comments for automobile upholstery dust extracts apply similarly to furniture upholstery dust. It is recommended that furniture upholstery dust be placed in Category IIIB.

30. *Dust, hay.* "Hay Dust" is too indefinite as a description of the source of material for extraction. It is recommended that hay dust extracts be placed in Category IIIB.

31. *Dust, prairie hay.* Prairie hay (*Graminae* spp.) is a mixture of pasture grasses, mostly of the family *Graminae*, but it is certain to contain a variety of unrelated plants. Like other hay dusts from well-defined plant species, it will also contain spores, pollen, bacteria, and other contaminants. The comments for "Dust, alfalfa hay" extracts also apply similarly to prairie hay extracts. It is recommended that prairie hay extracts be placed in Category IIIB.

32. Dust, *kafir.* Kafir is a variety of *Sorghum vulgare*, a sorghum grain grown for feed and also for silage. Like other gain dusts, there may be allergenic properties which are unique to the species, but the dust is certain to contain mold and basidiomycetes spores which are common to all grain dusts.

Additional studies would be needed to determine whether dust from kafir differs from other grain dusts as an allergen. It is recommended that

extracts of Kafir dust be placed in Category IIIB.

33. *Dust, lespedeza hay.* Lespedeza (*Lespedeza striata*) belongs to the family *Leguminosa* and is a plant grown for hay. Additional studies would be needed to determine whether dust from lespedeza hay differs from other farm dusts as an allergen. The comments for alfalfa hay dust extracts apply similarly to lespedeza hay dust extracts. It is recommended that lespedeza hay extracts be placed in Category IIIB.

34. *Dust, milo.* Milo is another variety of *Sorghum vulgare*, a sorghum grain, and is smiliar in appearance and related to kafir. Milo dust is irritating to the skin and respiratory tract for some individuals apart from its potential as an allergen. Additional studies would be needed to determine whether dust from milo differs from other farm dust as an allergen. It is recommended that milo dust extracts be placed in Category IIIB.

35. *Dust, oat.* Oat (*Avena sativa*) is an important cereal grain widely cultivated throughout the world. Like milo dust, oat dust seems to have nonspecific irritating properties, especially for the respiratory tract; but it also has potential as an allergen. Additional studies would be needed to determine whether dust from oats differs from other farm dusts as an allergen. It is recommended that oat dust extract be placed in Category IIIB.

36. *Dust, pea.* The dust from dried peas (*Pisum sativum*) would be expected to contain particles of material derived from the outer coating of the seed or from broken seeds. However, it would also contain spores and other contaminants similar to that found in other dusts of vegetable origin. Additional studies would be needed to determine whether dust from pass has unique allergenic properties. It is recommended that pea dust extracts be placed in Category IIIB.

37. *Dust, pencil.* Dust from pencils, presumably shavings from sharpening pencils, may be derived from a variety of manufactured products, and lacks adequate definition as a source for extracts. It is recommended that pencil dust extracts be placed in Category IIIB.

38. *Dust, poultry.* The Panel recognizes that poultry dust probably contains a variable mixture of potential allergens, the components of which can be found in other extracts. For this reason, the Panel concludes that poultry dust lacks adequate definition as a source material and extracts are not essential to the practice of allergy. It is recommended that poultry dust extracts be placed Category IIIB.

39. *Dust, rice.* When first harvested, rice (*Oryza sativa*) grains are encased in a tough hull and also an inner skin or bran coat. The polished rice which we eat has had both of these removed; and in the process, dust is produced. Workers in the industry and persons living close to rice processing plants would be exposed. Additional studies would be needed to determine whether dust from rice has unique allergenic properties. It is recommended that extracts of rice dust be placed in Category IIIB.

40. *Dust, road.* Road dust lacks adequate definition as a source material. Road dust extracts should be placed in Category IIIB.

41. *Dust, rye.* Rye (*Secale cereale*) is a cereal grain similar to wheat and barley. Unlike wheat, oats, and barley, rye flowers open for pollination. It is therefore difficult to keep varieties pure; and, for this reason, only a few kinds of rye are known. Like other grain dusts, there may be allergenic properities which are unique to the species. Rye dust is certain to contain contaminants common to other grain dusts, as well as particles derived from the grain itself. Additional studies would be needed to determine whether rye dust differs from other grain dusts as an allergen. It is recommended that rye dust extracts be placed in Category IIIB.

42. *Dust, soybean.* Soybean (*Glycine max*) is a legume rich in protein, oil, carbohydrate, vitamins, and minerals. Soybeans are widely used as human and animal food and are a valuable source of raw material used in a variety of ways in industry. Dust from the dried beans would be expected to contain particles derived from the outer coating and from broken beans, as well as other contaminants common to dusts originating from vegetable sources. Additional studies would be needed to determine whether soybean dust has unique allergenic properties. It is recommended that soybean dust extracts be placed in Category IIIB.

43. *Dust, timothy hay.* Timothy (*Phleum pratense*) is a valuable grass crop raised for hay. Being a cool-season plant, it is more commonly found in the northern states and in Canada. Timothy is not considered a satisfactory pasture grass unless mixed with hardier grass. Unless specially cultivated, pure timothy hay is not a likely product. The Panel recognizes the potential for unique allergenic properties in timothy hay, but additional studies would be needed to establish the existence of these. It is recommended that timothy hay extracts be placed in Category IIIB for both skin test diagnosis and immunotheraphy.

44. *Dust, wheat.* Wheat (*Triticum* spp.) is a cereal grain of which there are 14 species. Seven of these are grown in the United States, but only three are of special importance, *T. compactum, T. aestivum,* and *T. durum.* There are a number of varieties of each species. *T. aestivum,* or winter wheat, is bread wheat and is most widely grown in the midwestern states.

As with other grain dusts, the Panel recognizes the potential for allergenic properties which may be unique to wheat dust; however, additional studies would be needed to establish the existence of any other than those found in wheat. It is recommended that wheat dust extracts be placed in Category IIIB.

45. *Excelsior.* Excelsior strands are wood shavings, probably most often of pine, but lack precise definition. Refer to the discussion of wood dusts later in this document. It is recommended that excelsior extracts be placed in Category IIIB.

46. *Fern spores.* The ferns are divided into 12 families, the most common of which is *Polopodiaceae.* It includes many genera such as *Pteridium,* (the bracken), *Adiantum* (maidenhair), *Dryopteris* (woodferns), *Asplenium* (spleenworts), *Polypodium* (polypody, *Camptosorus* (walkingleaf), *Onoclea* (sensitive fern), and *Polystichum* (holly ferns). Some genera that belong to other families are: *Trichomanes* (filmy fern), *Lygodium* (climbing fern), *Ophioglossum* (adder's-tongue), and *Botrychium* (rattlesnake fern).

Ferns reporduce through a process called *alternation of generations.* They form neither flowers, pollen nor seed. Instead the mature fern develops spores in small bread-like cases on the undersurface of the leaves. When the spores ripen, the cases burst open; and the spores fall to the ground. Each spore then, under proper conditions, may develop into a tiny plant. This plant is different from the original fern and belongs to a different generation. This plant develops special tissues which produce male and female sex cells. The male cell comes from an organ called the *antheridium,* and the femal organ where the egg develops is called the *archegonium.* When the sex cells mature, the male cell, or *antherozoid* swims through the moisture on the plant to the female organ and fertilizes the egg. The fertilized egg then grows into a mature fern which forms spores completing the cycle. Although the fern spores do become airborne, (Ref. 34) there was no evidence found in the literature that they are allergenic to man, but they are potentially allergenic and are identifiable source materials for extracts. The Panel recommends that individual fern spore extracts with the species identified be placed in Category

IIIA for both skin diagnosis and immunotherapy.

47. *Fiber glass.* Fiber glass is an inorganic substance generally recognized to be biochemically inert and incapable of causing allergic responses even though particles of fiber glass are physically irritating. It is recommended that fiber glass extracts be placed in Category IIIB.

48. *Flax fiber.* There is no published evidence that flax *(Linum usitatissimum)* fiber, its dust or linen fabric prepared from it acts as an allergen. However, it is recognized as a potential allergen from an indentifiable source. The Panel recommends that flax fiber extracts be placed in Category IIIA for both skin test diagnosis and immunotherapy.

49. *Flaxseed.* Flaxseed (*Linum usitatissimum*) meal is used in certain foods, especially in some baked goods and breakfast cereals. Flaxseed also has been used in cosmetics and animal feed, and the oil derived from flaxseed is the linseed oil used as a base for paints and other products. Flax components have been discussed as allergens in earlier literature (Ref. 35 through 38).

Dermatitis is a common problem among people working with linseed oil. The oil is probably a primary irritant although oleoresins in the oil may be contact sensitizers as well. Nasal symptoms and asthma have been reported from inhalation of flaxseed dust, although it is stated that flaxseed dust has a relatively high content of oil; and the particles are therefore heavy and not easily airborne. Ingestion of flaxseed in foods may cause immunologically mediated gastrointestinal symptoms of vomiting, nausea, or diarrhea (Ref. 37).

No studies have been found supporting effectiveness for skin test diagnosis, but it seems evident from the cited literature that extracts of flaxseed are useful in detecting allergy caused by exposure to flaxseed. Flaxseed allergens have been known to produce serious systemic reactions in testing and should either be used for cutaneous testing with caution only after proper dilution for interadermal testing. Some firms only market the product in a dilute form because of the potential reactivity.

No well-designed, properly controlled studies supporting effectiveness of flaxseed extracts for immunotherapy were found. Allusions to effectiveness based on case reports have been published (Ref. 37). As with other seed extracts, the potency factor contributes to a rather high risk/benefit ratio. Furthermore, controlling exposure should be possible in most instances.

Opportunities for exposure to flaxseed in food, by inhalation and by contact do exist. Awareness of the problem has undoubtedly lessened the frequency of flaxseed as an allergic problem since the days of the early reports. Flaxseed is a potent sensitizer and, if there is exposure, allergic symptoms may develop in the susceptible individual. There is often a need for confirmation of diagnosis with a skin test but, since avoidance is generally practical, there is seldom a need for immunotherapy. It is recommended that flaxseed extract be placed in Category I for skin test diagnosis and in Category IIIB for immunotherapy because of the risk of reactivity in relation to expected benefits.

50. *Glue, (unspecified).* Unless specified as to type—the term "glue" lacks definitions as to source, therefore it is recommended that glue extracts from unspecified sources be placed in Category IIIB.

51. *Glue, animal.* For the listed animal glue extracts, the animal source species was not specified and nothing was defined about other manufacturing additives in the source material. The Panel presumes that the animal protein would be the proper allergen for preparing extracts, analogous to fish glue extracts as discussed below. It is recommended that extracts of animal glue extracts be placed in Category IIIB.

52. *Glue, fish.* Historically, fish glue has been an extremely potent antigen and serious reactions on exposure to glue have been reported. These included deaths from intradermal testing (Ref. 40) and severe constitutional reactions to testing with weak dilutions of fish glue (Refs. 39 and 41).

In more recent years, such reactions have become less common and, presumably, there is less exposure to fish glue because of the increased use of adhesive material derived from other sources. Persons with a high degree of sensitivity to fish would be expected to react to glue made as a by-product from fish parts. There is evidence to show that the same fish antigen extracts used in testing for edible fish would detect patients who might be sensitive to fish glue, (Ref. 39) thereby eliminating the need for extracts of fish glues.

Fish glue extract is apparently potent in skin test diagnosis but is not recommended for use since more safe and specific extracts of edible fish should aid in the diagnosis of fish glue allergy. Fish glue extract should be contraindicated for immunotherapy because of high risk/benefit ratio, because avoidance is practical and it is obtained from an undefinable source material. It is recommended that fish glue extracts be placed in Category IIIB.

53. *Glue, Liquid.* The most common commercial liquid glues are now made from synthetic resins. Source materials for these extracts were not specified and are not adequately defined. It is recommended that liquid glue extracts be placed in Category IIIB.

54. *Glue, Powdered.* Comments above for liquid glue apply similarly. It is recommended that powdered glue extracts be placed in Category IIIB.

55. *Gums, Vegetable.* A variety of vegetable gums are used in prepared foods and cosmetic products. These gums have been reported to cause allergic sensitization, but the importance of these as common offenders is uncertain. The gums most frequently suspected are acacia (gum arabic), karaya, and tragacanth. Guar and carbo are listed by some producers of extracts. Other gums are derived from quince seed, locust bean (carob seed), Irish moss (carrageenan), chicle, algin, agar, bassora, gelatin, ghatti, mesquite and pectin. Evaluation of possible gum allergy by skin testing requires employing several gums, since cross-reactions have not been studied. There is no information available concerning immunochemical studies on any of these gums (Ref. 42).

Gelfan reviewed vegetable gums associated with allergic symptoms and found that karaya gum, tragacanth, and gum arabic all were found to cause a variety of allergic symptoms such as asthma, urticaria, vasomotor rhinitis, and gastrointestinal reactions. These symptoms could be corroborated by positive skin tests and passive transfer reactions. Thus, evidence for the IgE mechanism has been confirmed for at least some of these gums (Ref. 43).

There are no data available regarding immunotherapy with vegetable gums.

Three commonly used vegetable gums, karaya gum, tragacanth and gum arabic have been demonstrated to have allergenicity based on direct and passive transfer tests. Other vegetable gums would be expected to have similar properties by analogy. As mentioned earlier, several gums should be used when testing for suspected gum allergy since cross reactions between the gums are not known. A recent report by Danoff et al. (Ref. 44) in which gum tragacanth in a hamburger was the causative factor illustrates that allergy to vegetable gum is a current problem. It is recommended that extracts of gum acacia (gum arabic), karaya and tragacanth be placed in Category I for skin test diagnosis and category IIIA for immunotherapy. Extracts of carbo gum

and guar gum should be placed in Category IIIA for both skin test diagnosis and immunotherapy.

56. *Hemp dust.* Hemp *(Cannabis sativa)* dust has been found to be a cause of byssinosis in workers exposed to hemp dust for extended periods of time (Refs. 45 and 46). The symptoms of byssinosis are easily distinguished from allergic symptoms and the Panel did not find documented reports that hemp dust will cause allergic sensitization.

The Panel found no evidence on extract of hemp dust either for diagnosis or treatment. The Panel recommends that hemp dust extracts be placed in Category IIIA for both skin test diagnosis and immunotherapy.

57. *Ipecac.* Berrens (Refs. 47 and 48) briefly mentions ipecac (*Cephaelis isecacuanha*) as an allergen indicating that it does cause positive skin reactions insensitive atopic people. How sensitization occurs and the clinical symptoms induced from exposure are not described. No data were found concerning effectiveness for immunotherapy.

Ipecac is not considered to be a frequent cause of allergic sensitization, but since there are data to show that such sensitization can occur and can be detected by skin tests, it is recommended that extracts of ipecac be placed in Category IIIA for both skin test diagnosis and immunotherapy.

58. *Jute.* Jute (*Corchoruscapularis* and *C. olitorius*) fiber is used to make twine, rope and woven into coarse cloth or burlap. Dust from jute fiber is a potential allergen. It is recommended that extracts of jute fiber be placed in Category IIIA for both skin test diagnosis and immunotherapy.

59. *Kapok.* Kapok is the fiber obtained from the tropical ceiba tree (*Ceiba pentandra*), botanically closely related to the cotton plant. The fibers are too short for weaving but are used as stuffing in cushions, pillows, sleepiing bags, mattresses and life jackets. Wagner and Rackemann (Ref. 49) found that aged kapok was allergenic but that new kapok was very low in allergenicity.

In spite of increased use of synthetic fibers as stuffing material, kapok is still occasionally found in certain articles. It contributes to the allergenicity of some lots of house dust (Ref. 50), but it has never been considered to be an important common environmental allergen.

Modern studies of kapok extracts have not been done, but Wagner and Rackemann (Ref. 49) found that the active principle of kapok was lost in dialysis and concluded that it was a small molecular weight substance. Dialysis of kapok extracts is therefore not recommended. Also, the best source of source material may be aged kapok rather than fresh kapok.

It is recommended that extracts of kapok be placed in Category IIIA for both skin test diagnosis and immunotherapy.

60. *Lampblack.* No information was found about lampblack as an allergen. It is sometimes a component of printer's ink. The source material is not defined and is not likely to be antigenic. It is recommended that extracts of lampblack be placed in Category IIIB.

61. *Lavender.* Lavender (*Lavendula vera*) is a bush with pale purple flowers. The flowers are prized for their fragrance which the dried flowers will retain for a long time. The flowers are used in sachets and to make perfume. Dried flower powder of lavender is a potential allergen obtained from identifiable organic sources. The Panel recommends that extracts of lavender flower by placed in Category IIIA for both skin test diagnosis and immunotherapy.

62. *Linen.* Linen is a fabric made from flax fiber. As a processed product it may contain undefined substances other than flax fiber. Flax fiber is a more reasonable source material for extracts. It is recommended that extracts of linen be placed in Category IIIB.

63. *Lycopodium.* Lycopodium (*Lycopodium spp.*) or club moss is a low growing spore forming plant. The spores are harvested to make powder. The powder has been used in the past to lubricate surgical gloves but is not commonly used today. Lycopodium is not mentioned as an allergen in standard textbooks on allergy. Lycopodium is a potential allergen obtained from an identifiable organic substance. The Panel recommends that extracts of Lycopodium be placed in Category IIIA for both skin test diagnosis and immunotherapy.

64. *Malt.* Malt is a food product resulting chiefly from the sprouting of barley (*Hordeum vulgare*) but also of other grains. In the process, the insoluble starch changes into the sugar, maltose; and two enzymes, diastaste and peptase, are released. Ratner and Gruehl (Ref. 52) showed immunological cross-reactivity between malt and a barley protein, hordein, in guinea pig experiments. No skin test data were reported. Malt is a potential allergen obtained from identifiable organic sources. The Panel recommends that extracts of malt be placed in Category IIIA for both skin test diagnosis and immunotherapy.

65. *Monsanto enzyme.* Monsanto enzyme as listed as an extract by some firms is an enzyme used in detergent washing powders. Pepys states that in 1966 derivatives of *Bacillus subtilis* containing proteolytic enzymes were added to detergents to produce biologic washing powders (Ref. 53). Three years later in the United Kingdom, pulmonary disease was noted among workers who had been exposed to the dust of these materials (Ref. 54). Bronchial provocation testing with enzyme solutions in three nonatopic workers who had been heavily exposed to the substances in the factory resulted in immediate and late asthmatic reactions accompanied by eosinophilia and leukocytosis but without fever. Similar inhalation tests in a healthy volunteer were negative. All three workers had strong positive immediate skin prick tests to alcalase and maxatase enzymes, and one showed a dual skin reaction (Ref. 55). Since then, asthma among factory workers involved in the production of the biologic washing powders has been described from many parts of the world (Refs. 56 and 57) and in the majority of reports, atopic individuals appear more readily affected than nonatopics, particularly when the exposure is minimal. The presence of IgE antibody in the serum against *Bacillus subtilis* enzymes has been demonstrated by the radioallergosorbent test. Higher levels of this antibody corresponded with the presence of positive skin prick tests to the enzyme.

There were no data found on the effectiveness of immunotherapy with extracts of *Bacillus subtilis*. There is substantial evidence that extracts of *Bacillus subtilis* enzymes are effective in skin test diagnosis of allergic conditions due to exposure to this substance. It is recommended that extract of *Bacillus subtilis* enzymes be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

66. *Newspaper, Newspaper mix (printed), newspaper print, paper mix and paper pulp.* Wood pulp can be prepared for making paper by mechanically grinding the wood into suitable fibers or by cooking wood chips with various chemicals. Newsprint is a processed material which may consist of a blend of three parts mechanically ground wood and one part of pulp made by cooking wood chips with calcium bisulfite. Residual bisulfite is removed by washing, although traces probably remain.

Ink from printing newspapers is a mixture of substances which may include finely ground lampblack with boiled linseed oil that contains a small

amount of soap and resin to make a thick paste.

Newspaper or newsprint is not discussed as an allergen in standard texts on allergy and no information was found concerning safety or effectiveness of extracts from this potentially widely variable source material. The Panel recommends that extracts of newspaper and newsprint, paper mix and paper pulp be placed in Category IIIB.

67. *Nylon.* Nylon is a polymer fiber made from hexamethylenediamine and adipic acid. It is considered by the Panel to be biologically inert. The Panel recommends that extracts of Nylon be placed in Category IIIB.

68. *Orris root.* In 1935 (Ref. 58), orris (*Iris germanica, Iris pallida, Iris florentina*) root was regarded as an important cause of allergic symptoms. Asthma, rhinitis, and contact dermatitis were all reported to be due to orris root, mostly found in cosmetics. After a time, orris root received so much notice as an allergen that cosmetic manufacturers virtually discontinued its use. By 1972, Patterson (Ref. 59) and also Solomon in 1978 (Ref. 60) declared that orris root is no longer a problem because it is so rarely encountered.

The early literature quoted in Coca, et al. (Ref. 73) gives evidence of effectiveness in diagnosis by positive skin test reactions in allergic individuals and anecdotally reports its use in therapy. Cutaneous reactions, according to Coca et al. elicited with test solutions of orris root of 0.001 to 0.01 mg nitrogen per cc are usually significant. Constitutional reactions with orris root extract were mentioned as a possibility.

Because of the historical data concerning the former importance of orris root as an allergen and because a few cosmetic preparations may still contain orris root, the Panel recommends that orris root extract be placed in Category IIIA for both skin test diagnosis and immunotherapy.

69. *Paper, carbon.* Carbon paper is a manufactured product and lacks definition as a source material for extracts. It is recommended that extracts of carbon paper be placed in Category IIIB.

70. *Paper, mix and paper, pulp.* See "newspaper print."

71. *Psyllium seed (Plantago psyllium).* Psyllium is a herb grown in Southern Europe and India. It produces a seed which has bulk laxative qualities and is used in medicines. No data were found concerning psyllium seed as an allergen. It is a potential allergen obtained from identifiable organic sources. The Panel recommends that extracts of psyllium seed be placed in Category IIIA for both skin test diagnosis and immunotherapy.

72. *Pyrethrum (Chrysanthemum spp.)* Pyrethrum is made from dried and powdered flowers. There are two types, Persian powder *(Chrysanthemum coccineum)* and Dalmatian powder *(Chrysanthemum cinerariaefolium).* Pyrethrum is used in many insecticide preparations and has been implicated in allergic responses (Ref. 61). Since the plant from which pyrethrum is derived is a member of the *Compositeae* family, it has shared antigenicity with other *Compositeae* species. Therefore, some patients allergic to ragweed and other *Compsiteae* species would also be expected to show an allergic response on exposure to pyrethrum.

Reports in the literature (Ref. 60) state that extracts of pyrethrum are useful in detecting allergy to exposure to pyrethrum. Immunotherapy with pyrethrum extract is not usually recommended since avoidance should be possible. Since pyrethrum is an identifiable allergenic substance, it is recommended that extracts of pyrethrum be placed in Category IIIA for both skin test diagnosis and immunotherapy.

73. *Rapeseed.* Rape *(Brassica napus)* is an annual plant cultivated for its leaves and used as temporary pasture crop. A small amount is grown for the production of its oil-bearing seeds. No data could be found concerning rapeseed as an allergen; however, it is a potential allergen obtained from identifiable organic sources. The Panel recommends that extracts of rapeseed be placed in Category IIIA for both skin test diagnosis and immunotherapy.

74. *Rayon.* Rayon is manufactured from cellulose, the usual source being either cotton linters on wood pulp. The cellulose is treated chemically in a variety of ways to produce rayon. Whatever the process, the cellulose is digested to form a sticky, sirupy mass which is then spun into fibers. Rayon is biochemically inert and is considered by the Panel to be incapable of causing an immunological response. It is recommended that rayon extracts be placed in Category IIIB.

75. *Rose.* Rose (*Rosa spp*) petals are used in making perfume and sachets. Rose pollen is not widespread because the plant is entomophilous.

A quote from Vaughan and Black (Ref. 62), states:

> Vaughan's experience differs from that of Wodehouse who has observed only two cases of pollinosis due to rose in over 2000 cases. He found 18 positive rose reactions and one positive apple reaction per 100 positive short rageweed reactions. In the majority of instances, further observation confirmed the etiologic significance of these reactions.

Aside from this reference, little can be found to show that rose petal derviations or rose pollen is an allergen. Rose plant derivations are potential allergens obtained from identifiable organic substances. The Panel recommends that rose petal extracts be placed in Category IIIA for both skin test diagnosis and immunotherapy.

76. *Rug.* There was no information found to distinguish rug extract from house dust extract. Rugs are manufactured products prepared from a variety of substances. The Panel recommends that rug extracts be placed in Category IIIB.

77. *Seamoss (Seaweed).* Seaweeds belong to the seven different phyla of algae in the subkingdom *Thallophyta.* The giant kelp and the gulfweed belong to the phylum *Phaeophyta,* or brown algae. The giant kelp is genuis *Macrocystis,* species pyrifera. The gulfweed is *Sargassum bacciferum.* Irish Moss (*Chondrus crispus*) is in the phylum *Rhodophyta,* or red algae.

Algin derived from seaweeds is widely used in food and drugs such as salad dressing and ice cream and in medicines as an agent to hold the ingredients of compressed tablets together.

Carrageenan, from Irish moss, is usually included in the list of vegetable gums.

There are no data to show that these substances are allergens or that extracts are useful in diagnosis or therapy. However, when an extract of sea moss is obtained from a species identified source material, it is recommended that it be placed in Category IIIA for both skin test diagnosis and immunotherapy.

78. *Senna. Cassia* is any one of a group of plants comprising more than 400 different species. Cassias from Africa and from India supply the senna, or dried leaves, used as a laxative. African *cassia* is *Cassia acutifolia.* India *cassia* is *Cassia angustifolia.* Wild senna found in the United States is *Cassia marilandica.* No reference to senna or cassia as an allergen could be found. However, since senna is a potential allergen and if obtained from species identified source material, it is recommended that the senna extract be placed in Category IIIA for both skin test diagnosis and immunotherapy.

79. *Silk.* Vaughan and Black (Ref. 63) recognize that exposure to raw silk may cause allergic symptoms and list three possible sources of the allergen, the silk fiber itself, its gum of glue "sericin", utilized in making the cocoon, and the pupa or silkworm (*Bombyx Mori*) itself. In a well-reference discussion in their textbook, these major points emerge:

Antigenicity is found in descending order of concentration in: (1) the silkworm (or pupa), (2) sericin, and (3) finished silk. They recommend making the extract from either the worm or from the crude silk which still contains sericin. Allergic symptoms can occur both among silk workers and wearers of finished silk products. Reported symptoms included asthma, rhinitis, urticaria and atopic dermatitis. Passive transfer tests were positive using sera from silk-allergic patients and symptoms could be reproduced by inhalation challenge.

Because of the introduction of synthetic fibers, silk is now less widely used than it once was, but it is still a potential allergen.

The Panel recommends that manufacturers should consider the use of either crude silk or the silkworm as the source material and should clearly state the nature of the source material in labeling. The labeling should also include a warning that silk extract may induce severe reactions in highly sensitive patients and should be properly diluted prior to use. Silkworm extracts are likely to be more potent on a w/v basis than crude silk. Although silk extract has been shown to be effective in confirming the diagnosis of silk allergy, avoidance is often possible. The Panel recommends that silk extract be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

80. *Sisal.* Sisal, or henequen (*Agave fourcroydes,* and sisalana (*Agave sisalana*) are tropical plants cultivated for fiber which is used in making rope and twine. No reference to sisal as an allergen was found, but it is a potential allergen obtained from identifiable organic sources. The Panel recommends that sisal extracts be placed in Category IIIA for both skin test diagnosis and immunotherapy.

81. *Spanish moss.* Spanish moss (*Dendropogon usneoides*) is a member of the pineapple family, *Bromeliacea.* It is a monocotyledonous family which belongs between the grass and lily families. It is the gray moss which hangs from various trees, especially the live oak, and may be found throughout the States south of Virginia and west to Texas and Mexico. It is widely distributed in tropical America. The following is quoted from Vaugham and Black (Ref. 64):

> Feder has found patients allergic to Spanish moss. Treatment was not satisfactory.* Metzger reports that the pollen is present in small quantities in the air near Tampa. Will extracts of this pollen, he observed two positive skin reactions among thirty persons who had symptoms during the period of pollination. He considered Spanish moss of no great importance. The moss is used in the south as a filling for cheap pillows.
>
> *Feder, J. M., Anderson, S. C., Personal communication.

Data were not found to substantiate allergenicity or use in immunotherapy other than the statement quoted above. In this limited reference, Spanish moss is not considered an important allergen. Furthermore, while it may be allergenic, its usefulness in diagnosis and therapy has not been well established. It is recommended that extracts of Spanish moss be placed in Category IIIB.

82. *Tobacco.* Tobacco is a member of the plant family, *Solanaceae;* species, *Nicotiana tabacum.* Leaves are collected, dried, and cured and widely used in the form of smoking tobacco, chewing tobacco, and snuff. Tobacco is also the raw material source for a number of chemicals, chiefly nicotine.

Tobacco smoke is a primary irritant of the tissues of the respiratory tract and has been implicated in pulmonary emphysema and neoplasms of the lung. The irritating nature of smoke obscures the evaluation of its potential as an allergen. The majority of patients with respiratory allergy seem to be aggravated by tobacco smoke, but it is not always clear whether allergic mechanisms account for the symptoms.

Justus and Adams (Ref. 65), using mice sensitized to tobacco leaf extract, could not elicit reactions with water-soluble tobacco smoke condensate but were able to demonstrate Type I hypersensitive responses by mast cell degranulation when the sensitized mice were challenged with tobacco leaf extract. This suggests that the allergens of the leaf are not found in the smoke, at least when the mouse is used as a model for tobacco hypersensitivity.

Zussman presents evidence to show that tobacco allergy does occur and can cause symptoms of asthma and allergic rhinitis (Ref. 66). Sixteen cases were studied, all having some form of respiratory symptoms on exposure to tobacco smoke and all giving positive skin reactions to tobacco leaf extracts from Hollister Stier and Center Laboratories. Positive passive transfer tests were obtained with sera from four of the patients. Zussman (Ref. 66) also reported the treatment of 53 patients with excellent results in 33 (63 percent) and fair to good results in 20 (37 percent). All of the patients experienced some degree of symptomatic relief based on evaluation of the patient's subjective response to tobacco smoke before and after treatment with tobacco antigen.

Blue (Ref. 67) reports on 30 individuals with bronchial asthma who, by clinical tests or history, indicates that tobacco and its smoke either markedly aggravated or precipitated their symptoms. Twenty-two out of 30 of these individuals showed positive intradermal tests to tobacco and of these, 20 complained that their symptoms were precipitated by smoking or exposure to smoke and of these, 12 improved on elimination of smoking. The eight individuals who gave negative intradermal tobacco skin tests to leaf extract also noted that their symptoms were precipitated by smoking or exposure to tobacco smoke. Six of the eight improved on elimination of tobacco.

The author points out that tobacco smoke has a triple effect in that it has a pharmacological effect, acts as a chemical irritant, and has the potential to be an allergen.

On the other hand, several studies lead to the conclusion (Refs. 74, 75, and 76) that tobacco smoke allergy was not demonstrable in patients studied by RAST and skin testing. RAST, therefore, did not show tobacco antigen-specific IgE binding. Skin tests with tobacco smoke antigen revealed positive reactions in seven of 15 patients, but no correlation was found between skin test results and occurence of symptoms. Sera from skin-test-positive subjects reacted to tobacco antigen significantly greater by RAST than sera from skin test negative subjects. However, this finding was minimal and could not be inhibited by preincubation of sera with tobacco antigen and therefore was judged to be nonspecific.

It is difficult to reconcile these conflicting data. It is apparent that positive skin reactions will occur with tobacco antigen, but the skin test data of McDougall (Ref. 68) would suggest that the skin tests do not clearly detect IgE-mediated sensitivity. Even though RAST may not be the ultimate tool for diagnosing allergy, McDougall's data did not provide convincing evidence that allergy to tobacco does not exist using this technique. Even so, tobacco is an organic substance and at least should be expected to contain allergenic substances.

In the manufacturing process for extracts, ground leaves are defatted and extracted in a buffered extracting fluid. Dialysis is necessary to remove small molecular weight alkaloids which interfere with skin testing.

Since tobacco is a member of the Solanacea, other plant members, namely eggplant (*Solanum melongena*), green pepper (*Capsicum frutescens*), potato

(*Solanum tuberosum*), and tomato (*Lycopericon esculentum*), were studied by Becker (Ref. 69) who showed that each contained a cross-reactive glycoprotein, molecular weight approximately 18,000 Daltons, similar to that found in tobacco leaf and tobacco smoke. Upon testing with this tobacco glycoprotein (TGP) in 31 human volunteers, of 12 skin test positive individuals, six were smokers and six were nonsmokers. Of 19 skin-test-negative individuals, nine were smokers and 10 were nonsmokers. It was suggested that the high incidence of cutaneous reaction to tobacco glycoprotein was a function of the ubiquity of the antigen rather than nonspecificity, since the antigen is both in smoke-contaminated air and in vegetables which are commonly eaten.

The Panel found no data showing evidence of favorable immunologic response to treatment with tobacco antigen and no reports of controlled double-blind studies showing that tobacco antigen would relieve symptoms better than placebo. Evidence for an active antigen in tobacco leaf, tobacco smoke and several related vegetables is convincing. However, correlation of skin reactions with clinical symptoms is not so convincing and tobacco antigen has not been widely accepted as an allergen probably because of the chemically irritating properties of the smoke mentioned earlier. Further investigation is needed to establish the importance of tobacco as an allergen. The Panel can conclude by analogy to other immunologically active organic substances that tobacco leaf extract has potential usefulness in diagnosis and also may be useful in treatment of patients with allergic symptoms due to exposure to tobacco leaf dust.

The Panel recommends that green tobacco leaf extract be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy. Extracts of cured tobacco leaf should be placed in Category IIIA for both skin test diagnosis and immunotherapy. Tobacco smoke extracts should be placed in Category IIIB because the carcinogenic potential has not been evaluated. Extracts of cigar tobacco, cigarette tobacco, tobacco mix, pipe tobacco, and snuff are from poorly defined sources and should be placed in Category IIIB.

83. *Wood dusts.* Wood dust can be a hazard for hobbyists and professional wood-workers. Both contact dermatitis and respiratory allergic symptoms have been reported to occur as a result of exposure. Fine wood dust can also act as a primary respiratory irritant in some instances. A number of wood dust extracts from different tree species are offered for use in allergy. There are insufficient data on many of them. There are also reports in medical literature concerning some dusts which are not listed in manufacturers' data submissions.

The Panel has selected oak and cedar as examples of allergenic wood dusts since there is information to show that they have allergenic properties.

There is a single case report (Ref. 70) of one man with a demonstrated sensitivity to tannic acid manifesting symptoms of asthma, rhinitis, and urticaria on inhalation of a spray containing tannic acid. He also had asthma from drinking iced teas and from inhaling oak saw dust. Positive skin reactions were obtained from 1:1,000 tannic acid, egg albumin-tannate, and an extract of oak saw dust. Passive transfer tests using the patient's serum were positive on 12 subjects in dilution up to an including 1:1,000,000 UPS tannic acid. Cross sensitivity to gallic acid was found in five out of six recipients of the patient's serum and to pyrogallol in one out of three on whom it was tried. Resorcinol, pyrogallol triacetate, and pyrogallol 1,3 dimethyl ether gave negative reactions in all subjects. There are no data in this report about therapy since the patient was successfully treated by avoiding contact with tannic acid and oak dust.

Mue, et al. (Ref. 71) reported on 17 workers who suffered from asthma after working with western red cedar (*Thuja plicata donn*). Volative substances were removed from odoriferous western red cedar saw dust and an aqueous extract was made. The resulting crude extract was separated into four fractions by a series of filtrations, dialyses and ammonium sulfate precipitations. Direct skin tests on the workers and P–K tests were done using the asthmatic workers' sera. Fraction 3 made from the crude aqueous extract was prepared from the 50 to 60 percent saturated ammonium sulfate precipitate and was suspected of containing a glycoprotein. Fraction 3 seemed to be the most active skin test reagent by direct and P–K testing. It had no odor, smell or taste except that of saline after reconstitution. Inhalation challenge with fraction 3 produced typical asthmatic symptoms in the subjects. The volatile components were tested by skin tests and by inhalation trials. The skin tests were negative and inhalation of the substances produced coughing; however, it did not result in asthamatic attacks. On the basis of this study, the authors conclude that there exists an antigen in the sawdust of western red cedar which can produce allergic asthma among exposed workers.

There is evidence of respiratory allergy to such exotic woods as cocabolla, kejaat, and padauk (Ref. 72). Three patients were found with respiratory symptoms attributable to allergy to cocabolla. Two gave immediate wheal and flare reactions on prick testing with an aqueous 2 percent solution. Skin testing with this extract on allergic subjects not exposed to cocabolla or allergic to cocabolla was negative in 10 cases and also negative in 10 nonallergic cases not exposed to this wood. Injection treatment with aqueous extracts of padauk and cocabolla in one case and with cocabolla in another was followed by the disappearance of immediate skin sensitivity on prick testing with extracts of cocabolla in both and padauk in one. There appeared to be clinical improvement as well. Saponins or quinones were mentioned as the possible allergens in cocabolla wood. It would appear that active organic compounds such as quinones, found in wood dust, can act as haptens combining with body proteins, so that the hapten-protein conjugates become allergens. This would also seem to be true in the case of oak (Ref. 70).

Other woods have been observed to cause symptoms of respiratory allergy. These include mahogany, birch, tamarack, and pine (Ref. 73). Unfortunately, supporting data are not given concerning skin test efficacy or therapy.

There are no data, but it would be presumed there is shared antigenicity between related species of wood as there is between pollen from related trees.

The Panel concludes that there are data to show that oak, cocabolla, cedar and padauk extracts are not irritating to normal skin and cause positive skin tests in patients with sensitivity to the respective woods. Information was also presented about treatment with cocabolla and padauk extracts which was associated with loss of immediate skin reactivity in two patients and loss of contact hypersensitivity in another. Wood dusts of other species have been shown to be a cause of allergic symptoms in selected cases, but substantial data for most varieties of wood dust extracts offered by manufacturers are lacking about effectiveness for skin test diagnosis and therapy.

The Panel recommends that the labeling of each wood dust extract list the species of origin. It is recommended that extracts of cedar (*Thuja plicata*),

cocabolla, oak and padauk wood dusts be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy. Extracts of other wood dusts should be placed in Category IIIA for both skin test diagnosis and immunotherapy.

Other extracts of miscellaneous substances. Other extracts of various undefined substances may have been prepared by some manufacturers but for which no data were submitted to the Panel. Until evidence of allergenicity, safety, and effectiveness are submitted, it is recommended that other extracts made from undefined source materials be placed in Category IIIB.

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E. House Dust and Similar Extracts

1. *Introduction.* Dust is "earth or other solid matter in a minute and fine state of subdivision, so that the particles are small and light enough to be easily raised and carried in a cloud by the wind" [Ref. 1). House dust is dust which is present in buildings usually inhabited by humans, i.e., in homes and apartment houses. It is, of course, not confined to such sites; dusts of similar composition can exist in hotels and motels, for example.

House dust has long been recognized as a cause of respiratory symptoms, yet physicians still differ in their judgment of what they will diagnose as pure house dust allergy. In the decades since the first reports of wheal-and-flare reactivity occurring in allergic patients after intradermal injections of extracts of house dust (Refs. 2 and 3), an enormous amount of investigation has been carried out in order to unravel the elusive nature of the allergens in house dust and to establish the effectiveness of these extracts in the diagnosis and therapy of allergic disease. While significant progress has been made, many questions still remain unanswered. Principle among them is whether there is in fact an allergen which is unique to house dust.

2. *Clinical aspects of allergy to house dust.* Patients with allergy to house dust are usually described as having perennial rhinitis, with or without asthma. Sheldon et al. (Ref. 4) state that it is the most common cause of perennial allergic rhinitis. In a typical case, the patient will give a history of sneezing, rhinorrhea, lacrimation, and dyspnea when cleaning house. Many asthmatics become more wheezy when sweeping floors, making beds, or beating rugs. Evidence connecting house cleaning with attacks of asthma was provided by Clark et al. (Ref. 5), who found that increased concentrations of airborne particles of 2 micrometers and less, e.g., those generated by vacuum cleaning or sweeping, occurred within 2 minutes of cleaning and were associated with rapid onset of airways obstruction in dust-sensitive asthmatic subjects. The symptoms of house dust allergy are frequently worse in winter (Ref. 6), and patients may report that they are less symptomatic when out of doors (Ref. 4). Attacks of asthma in house-dust-sensitive patients are said to occur frequently at night and during the early morning hours (Ref. 7).

The Panel found no report describing the natural history of allergy to house dust in untreated patients.

Allergy to house dust is probably the most common immediate hypersensitivity diagnosed in clinical practice. Perhaps as an extreme example, Fontana et al. (Ref.8) reported that 88 percent of allergic patients and 42 percent of nonallergic patients had a positive skin reaction to house dust extract. In general, the prevalence of positive reactions to house dust certainly exceeds that reported for other allergens, as cited elsewhere in this document. However, the unavailability of standardized house dust extracts and the inability to arrive at a generally acceptable definition of pure house dust allergy leaves the significance of this high rate of skin reactivity open to question.

The relatively localized nature of the individual patient's exposure to dust in his own home led physicians to recommend various environmental measures aimed at reducing the amount of dust to which the patient was exposed (See, for example, Refs. 9 and 10). The extent of environmental manipulation recommended by physicians varies widely. The effectiveness of these procedures, which supports the existence of the disease entity itself, is not doubted by most allergists, although effectiveness has never been established by a controlled clinical trial. In fact, the British Tuberculosis Association (Ref. 11) reported that patients who were given advice on house dust control in their homes did not fare any better than those who did not receive such advice. Clearly, to be effective, avoidance procedures should be aimed at

specifically identifiable allergens. As presented more fully below, Voorhorst et al. (Ref. 12) in studies conducted in Europe advocate the view that a substance (or substances) elaborated by the mite *Dermatophagoides pteronyssinus* is the principal allergenic component of house dust. In one study (Ref. 13), reduction of the mite population in households by environmental control measures was associated with less asthma in 14 dust-sensitive children. That the environmental measures in this uncontrolled study probably reduced the amount of other allergens as well does not invalidate the hypothesis, although it does leave it still open to question.

House dust extracts are widely used in clinical practices to treat patients with a history of house dust sensitivity which is confirmed by a skin test, as discussed more fully below. The use of these extracts in therapy is described in standard textbooks on allergy (See, for example, Refs. 4, 9, and 14).

3. *Product description.* In contrast to the majority of allergenic substances, house dust samples are not defined or pure substances, but are mixtures of many substances which are present in the environment of dust-sensitive patients.

The source material used in the production of these extracts varies from manufacturer to manufacturer, according to information submitted to the Panel by the manufacturers. In one instance, house dust consists of material obtained from vacuum cleaners used in homes that do not contain house cats, dogs, birds, or other pets. In some cases, material vacuumed from mattresses and stuffed furniture is used. Carpet sweepings are used by at least one manufacturer. In some cases, kapok and feathers are added to the dusts to "fortify" the source material. Linters, including those collected during the ginning of cotton and from mattresses, are used by some manufacturers. One manufacturer obtains dust from a hotel and various apartment houses.

Several manufacturers prepare autogenous dust extracts (*infra vide*) from dust collected in individual patients' homes. This is usually procured by vacumming, as described by Sheldon et al. (Ref. 4). Each collection of autogenous dust from a given home is obviously a unique conglomerate mixture.

House dust extract is manufactured by a variety of procedures. The source material may or may not be defatted with an organic solvent after being stored for variable periods of time under widely differing conditions. Extraction is carried out in aqueous or glycerinated solvents for 1 to 3 days at room temperature or in the cold. This step may be followed by dialysis. In some cases, extraction and dialysis is followed by precipitation with an acetone solution. One manufacturer follows a procedure originally described by Boatner and Efron (Ref. 15).

House dust extracts are available in aqueous and glycerinated solutions, in dilutions ranging from 1:10 to 1:100,000,000 and up to 20,000 PNU/mL. Lyophilized house dust extract is listed by at least one manufacturer.

4. *Composition*—a. *Nature of the allergens in house dust.* The allergenic character of house dust has been the subject of several reviews and at least one doctoral thesis during the past 40 years (Refs. 16 and 20). The properties of house dust have been studied in a number of ways. In one approach, the assumption is made that the allergenic activity of house dust is due to a single one of its many constitutents. A search is made or various possible components of house dust allergen (for example, cat dander, *D. pteronyssinus,* etc.) and the activity of extracts prepared from these individual components is compared to that of an extract of whole house dust in house dust-sensitive individuals. One limitation of this approach is the possibility that the allergenic principle may either be formed by the interaction of various constituents of house dust or be generated by action of microorganisms (bacteria and fungi) on various constituents of house dust. In another approach, allergenically-active batches of house dust are subjected to exhaustive separative procedures in an attempt to isolate and characterize the skin-reactive principle(s) in highly purified form. Both approaches have been hampered by the lack of a clear definition of house dust allergy and by lack of a well-defined, consistent, source material (Refs. 21 and 22).

A considerable amount of research has been undertaken to determine whether there is indeed a unique house dust allergen or whether the skin test reactivity of house dust can be attributed to as specific substance. It is commonly observed in atopic individuals that the incidence of positive wheal-and-flare reactions and positive bronchial challenge reactions to house dust exceeds that of other allergens tested.

An unresolved question is whether there is an additive effect of different allergens incorporated in a single house dust extract when tested in patients with multiple sensitivities (Ref. 24). In addition to a high incidence of wheal-and-flare reactions when house dust extract is tested in an atopic population, there is much evidence that concentrated extracts of house dust, more than other allergen, give an inordinantly high incidence of positive skin test reactions in non-allergic individuals (Refs. 8, 21, and 25 through 27).

(1) The following examples support the position that many individual substances can be found in house dust:

(i) Materials of plant origin have been implicated by Berrens (Refs. 21, 28 and 29) and McEwen (Ref. 30), more specifically from cotton and cotton linters by Berrens (Ref. 31), Cazort (Ref. 32), Cohen et al. (Ref. 33), Davidson (Ref. 34), Follensby (Ref. 35), Hale and Cawley (Ref. 36), McEwen (Ref. 30) and Foubert and Stier (Ref. 37); from Kapok by Berrens et al. (Ref. 31) Davidson (Ref. 34) and McEwen (Ref. 30); from hay by Berrens et al. (Ref. 31); and from flax, orris root, pyrethrum and tobacco by Davidson (Ref. 34).

(ii) Bardana et al. (Ref. 38) have demonstrated an *Aspergillus* component in house dust. Davies (Ref. 39) found 55 species of 28 fungus genera in house dust, 19 species of 13 genera being capable of colonizing the dust. No influence on house dust reactivity due to these fungi could be shown. Graveson (Ref. 40) suggested that certain microfungi may play a role in the degradation of textile fibers and the skeltons of dead mites in house dust, thereby contributing to the complexity of this material.

(iii) Baldwin et al. found members of seven bacterial families in dust with an average count of 1,802,850 bacteria per gram and discussed the possible metabolic changes produced by these bacteria (Ref. 41).

(iv) The presence of allergenically reactive dander components in house dust has been widely covered in the literature, including human dander by Berrens (Refs. 21, 28, 29 and 31), Davies (Ref. 39), Monard and Geubelle (Ref. 42), Dasgupta and Cunliffe (Ref. 43), Wolfenberger et al. (Ref. 44); horse dander by Davidson (Ref. 34); cat and dog dander by foubert and Stier (Ref. 37): cat dander by Trinca et al. (Ref. 45); cat, dog and human dander by Hampton and Stull (Ref. 46).

(v) A feather component may be allergenically active in house dust as reported by Berrens et al. (Ref. 31), Davidson (Ref. 34), Hampton and Stull (Ref. 46), McEwen (Ref. 30), and Foubert and Stier (Ref. 37). Other possible allergenically active components have also been shown including wool by Berrens et al. (Ref. 31), Davidson (Ref. 34), McEwen (Ref. 30) and Foubert and Stier (Ref. 37); silk and glue by Davidson

(Ref. 34); animal hairs by Davidson (Ref. 34) and McEwen (Ref. 30); and cockroach by Morita et al. (Ref. 47). The presence of human blood group substances in house dust also has been demonstrated by Brocteur and Versie (Ref. 48) and Rimington (Ref. 49).

(2) Further evidence of the heterogeneity of house dust has been demonstrated both immunologically and allergenically:

(i) Antigenic cross-reactions of house dust extract and extracts of other allergens have been demonstrated by various immunological methods: to dandruff, cotton, kapok, feathers and wool by Berrens and Versie (Ref. 50); to feathers, dog, cat and human danders by Hampton and Stull (Ref. 46); to cotton linters by Coulson and Stevens (Refs. 19 and 51); to *Aspergillus* by Pavlinae (Ref. 52); to *Escherichia coli* endotoxin by Peterson (Ref. 53); to human albumin, IgA and IgG by Versie and Brocteur (Ref. 54) and to human dander by Wolfenberger et al. (Ref. 44).

(ii) House dust extracts have been shown to cross-react allergenically with cotton linters by Cohen et al. (Ref. 33), Follensby et al. (Ref. 35), Hale and Cawley (Ref. 36) and McEwen (Ref. 30); with feathers by Halpin and Prince (Ref. 55), McEwen (Ref. 30) and Voorhorst (Ref. 56) (slightly cross-reacting); with fungi by Pavlinae (Ref. 52); with kapok by Voorhorst (Ref. 56) (slightly cross-reacting).

(3) That many of the substances listed above must occur in house dusts throughout the world could account for cross-reactions demonstrated between various house dusts:

(i) Extracted dusts from different geographical locations have exhibited antigenic cross-reactions as reported by Dasgupta and Cunliffe (Ref. 43), Hampton and Stull (Ref. 46), Hanissian et al. (Refs. 57 and 58), Kohler-Kubelka and Mimica (Ref. 59), Phillips and Northey (Ref. 60), Van Dishoeck and Voorhorst (Ref. 61), Vannier and Campbell (Ref. 62) and Wlfenberger et al. (Ref. 44).

(ii) Extracted dusts from widely different geographical locations and from different sources have been demonstrated to cross-react allergenically by Berrens et al. (Ref. 31), Coulson and Stevens (Ref. 10), Frankland and El-Hefny (Ref. 63), Hanissian et al. (Ref. 58), Hosen (Ref. 64) (but not between Endo and Center dust extracts), Kohler-Kubelka and Mimica (Ref. 56), Lietze and Reed (Ref. 65), May et al. (Ref. 66), McEwen (Ref. 30) (mattress dust with old animal keratin, but not with old cotton or kapok), Milner et al. (Ref. 67) (quantitative, but not qualitative differences), Monard and Geubelle (Refs. 42 and 68), Ordman (Refs. 69 and 70) (coastal and highland dusts), Özkaragöz and Cakin (Ref. 71) and Prince et al. (Ref. 72) (house, hotel, store, office, and dormitory dusts).

(4) A review of the literature dealing with attempts to identify individual allergenic components of house dust indicates the following to be among the most likely candidates:

(i) *Cotton linters.* Extracts prepared from cotton linters have been studied by at least two groups (Refs. 15, 33, 51, 73, and 75 through 79). Evidence was presented by Boatner et al. (Refs 15, 75, and 76) indicating that skin-reactive material was obtainable only from cotton that had undergone aging by storage and that skin-reactive materials could not be found in freshly ginned cotton. Cotton dust extracts were reported to contain a dialyzable histamine liberator (Ref. 77). The Panel found no reports of recent studies of the allergenic activity of cotton linters. Refer to the section on "Miscellaneous Inhalant Extracts" for additional comments on cotton linter extracts.

(ii) *Kapok.* This vegetable fiber was at one time considered to be an important allergenic component of house dust, and a substantial incidence of positive reactions to kapok was demonstrated in house-dust-sensitive individuals (Refs. 78 and 79). By analytical and physiochemical criteria, allergens isolated from kapok were reported to resemble purified dust allergens in that both appeared to be a heterogeneous mixture of degraded plant glycopeptides (Ref. 80). However, this report has not been confirmed. The decreasing presence of kapok in recently manufactured household goods without a concomitant decrease in reactivity to house dust extract suggests that kapok is not a significant component of house dust. Refer to the section on "Miscellaneous Inhalant Extracts" for additional comments on kapok.

(iii) *Mold spores.* Mold spores are well-recognized sources of allergens present in house dust. Still, the significance of molds in house dust has not been determined.

(iv) *Animal danders.* House dust usually contains materials of animal origin. Cat dander, in particular, has been regarded as one of the important allergens in house dust. In a recent study (Ref. 24), it was reported that patients giving positive skin reactions to house dust extract but negative reactions to *Dermatophagoides* were usually allergic to cat dander extract. This did not prove that cat allergens were in the dust.

(v) *Feathers.* Chicken, duck, and goose feathers, after an aging process, have also been suspect as the house dust allergen (Refs. 33 and 73). While there is a high incidence of positive skin tests in house-dust-sensitive patients tested with extracts of feathers, the incidence is not regarded as sufficiently great to implicate feathers as the sole house-dust allergen (Ref. 55). In addition, chemical analysis of feather allergens has shown them to be substantially different from allergens in house dust (Ref. 81). Refer to the section "Extracts of Mammalian and Avian Origin" for additional comments on feather extract.

(vi) *Human dandruff.* Human dandruff has long been considered as a possible allergenic component of house dust (Refs. 29 and 82 through 88). It is one of the most abundant airborne particles in home air (Ref. 89). Furthermore, one study of sieved house dust found it to contain as much as 90 percent human dander (Ref. 90). Because of its human origin, there has been some reluctance to accept dandruff as a significant allergen of house dust. There do appear to be allergens in extracts of human skin scales which are not present in extracts of house dust. Human dander has by no means been excluded from contributing to the allergenicity of house dust.

(vii) *Arthropods.* A variety of arthropods have been recognized as potentially contributing to the allergenicity of house dust (Refs. 16 and 91). These allergens appear to be derived from scales or dust shed from the wings or body of the insect, or from their excreta. A high incidence of positive skin tests to aqueous extracts of arthropods has been recorded in house-dust-sensitive people, particularly persons in certain geographic locations (Refs. 92 and 93).

In the past decade, numerous publications have appeared on the contribution of mites (order *Acarina*) to the allergenicity of house dust (reviewed in Ref. 14). The evidence for mites as a principal allergenic component of house dust is based upon (1) a relationship between mite counts in dust samples and potency of extracts prepared from the samples; (2) the correlation between potency of dust extracts and environmental conditions favorable for proliferation of mites; (3) the finding that excreta of mites collected from the walls of glass culture vessels contain a potent skin test allergen; (4) the almost universal finding of mites in house dust collected in all parts of the world; and (5) the high incidence of positive skin test reactions to mites in house-dust-sensitive individuals (Refs. 12, 16, 85, 94, and 95).

Two species, *Dermatophagoides pteronyssinus* and *D. farinae (culinae)*

are regarded as the most common offenders, their presence varying by goegraphical locations. Evidence for and against both species has been complied by many techniques including histamine release from human leukocytes, histamine release from lung tissues, the results of immunotherapy, bronchial inhalation challenge, nasal provocation skin tests, immunodiffusion, immunoadsorption, skin window techniques and overwhelming presence of mites in dust samples (Refs. 12, 13, 43 through 45, 47, 85, 87, 94, and 97 through 134).

A recent analytical review, with which the Panel agreed, concluded that the active components derived from mites represent just another class of allergens in house dust (Ref. 74).

b. *Chemistry.* The chemical nature of the allergenically active material in house dust has been studied by many investigators who have variously described it as: (1) A protein: Versie et al. (Refs. 22 and 54); (2) a mucoprotein or glycoprotein: Berrens et al. Refs. 21, 28, and 31), Guibert et al. (Ref. 135), and Lietze and Reed (Ref. 65); (3) a carbohydrate and protein complex: Boatner and Efron (Ref. 15), Monard and Geubelle (Ref.42), Morris et al. (Ref. 136), and Rimington et al. (Refs. 49 and 137); (4) a polysaccharide with an amino sugar comstituent: Campbell et al. (Ref.138); and (5) a polysaccharide-polypeptide complex: Gross (Ref. 139), Vannier and Campbell (Refs. 62 and 140), but it will not be worthwhile to study the chemistry of house dust components until each has been isolated and purified.

As noted in the section on "Safety," house-dust extracts are known to contain endotoxin. See also Reference 151.

5. *Standardization.* House dust extracts are marketed either in terms of weight-by-volume or protein nitrogen units. There is no standard of potency for these products and no comparison is made of skin reactions produced by any particular batch or lot with reactions produced by a reference batch. No information was provided by the manufacturer on reproducibility of skin reactions with different lots of home dust extracts. No information was provided on the determination of composition or potency by in vitro techniques. No information was provided on the stability of house dust extracts.

6. *Labeling.* Refer to the general section on Labeling.

7. *Safety.* The manufacturer submitted no significant data on short-term or long-term safety of house dust extracts. The Panel found no controlled or partially controlled studies on the specific question of the safety of house dust extracts. Although endotoxin content in some house dust extracts has been found to be high, there is no evedence that it is a hazard. Refer to the section on Safety for additional comments.

8. *Effectiveness*—a. *For diagnosis.* House dust extracts is employed extensively in medical practice for diagnosis. A large number of studies of allergy in general and asthma in particular have included house dust extract to confirm the diagnosis of allergy to house dust. A smaller number of studies have addressed the question of specificity of house dust extract in diagnosis. However, in none of these studies was the potency of the extract reported, nor is the description of the study population adequate.

Lindblad and Farr (Ref. 26) skin tested 100 nonallergic subjects with house dust extract and found that 50 percent reacted to undiluted extract, 19 percent to a 1:10 dilution, and 4 percent to a 1:100 dilution of the extract. Sera from four individuals who reacted to the 1:10 dilution contained detectable skin sensitizing (IgE) antibody.

Fontana et al. (Ref. 8) skin tested 100 allergic children and 100 nonallergic children with house dust extract and found a positive reaction in 88 percent of the former group and 42 percent of the latter group.

Kang and Sulit (Ref. 141) used 50 percent glycerinated house dust extract (1:10 w/v, Hollister-Stier) in intracutaneous tests when the prick test reaction was less than 8 millimeters (mm) in diameter. The frequency of positive skin test reactions was 72 percent in 155 atopic adult subjects, 78 percent in 67 atopic children, and 57 percent in 63 nonatopic children. Of 105 adult asthamatic subjects, 79 percent had a positive skin reaction, and of 48 children with asthma, 88 percent had a positive skin reaction to house dust extract.

Siraganian et al. (Ref. 151) performed *in vitro* histamine release studies with leukocytes from 15 dust-sensitive subjects, employing eight different lots of house dust extracts from seven manufacturers. With one potent extract, the concentration (in PNU per mL) required for 30-percent histamine release ranged from 0.002 in the most sensitive subject to 12.33 in the least sensitive. The most potent extract was almost 1,000-fold more potent than the least potent extract; with the leukocytes of some subjects it was much greater than 1,000-fold.

Berg et al. (Ref. 142) found an overall agreement of 72 percent between nasal and bronchial provocation tests and RAST in dust-sensitive patients.

Aas and Johansson (Ref. 143) compared the results of mucosal provocation tests with skin tests and RAST in dust-sensitive children. Using positive or negative bronchial, nasal, and conjunctival provocation tests with the extract to define house dust allergy, they found that the skin test accurately diagnosed the allergy in only 34 percent; RAST was accurate in 59 percent. This was attributed to the heterogenicity of the allergens extracted from house dust and to the lack of satisfactorily purified and standardized extracts.

On the basis of these and other studies, the Panel concluded that positive skin test reactions to various unstandardized house dust extracts occur in patients with rhinitis and/or asthma to a greater extent than in control nonallergic subjects. Serological tests including RAST have confirmed the presence of IgE antibodies to dust in clinically sensitive patients and/or in patients with positive skin tests to house dust extract. Sensitivity to dust has been confirmed by mucosal provocation tests. The Panel was unable to determine to what extent mucosal provocation reactions to house dust extract may have been due to a nonspecific (i.e., nonimmunologic) reaction.

Positive skin tests with house dust extract, particularly when used in higher concentrations and administered intradermally, do occur in individuals who deny a clinical history of allergy to house dust. Some of these reactions may have a reaginic basis.

b. *Effectiveness for therapy.* Studies on the efficacy of house dust in the treatment in inhalant allergic disorders are difficult to compare because of the lack of information concerning the composition and potency of the extract used in the treatment regimen. The potency of the extract is certainly significant; one study indicated that immunologic changes following administration of house dust extract occurred only with doses considerably larger than those customarily administered (Ref. 66).

Bruun (Ref. 145) attempted the first controlled study of the effect of immunotherapy with house dust extract in asthmatic adults in whom allergy to house dust was thought to be important. The study group consisted of 189 patients, about half of whom were placebo-treated controls. While by present standards this is an imperfect study, 78 percent of the treated group was reported as improved, compared with 34 percent of the untreated control group. In a followup crossover study, the

previous placebo group was given injection of house-dust extract, and they also showed improvement.

Aas (Ref. 146) studied 80 children with asthma in what probably is the most thorough evaluation of house dust immunotherapy to date. Both clinical status and bronchial reactivity to house dust extract was evaluated. The extracts were administered over a 2-to-3-year period. The house dust-extract-treated group showed a significant decrease in bronchial reactivity which was roughly correlated with clinical improvement.

McAllen (Ref. 147), on the other hand, in a study of the effect of treatment with house-dust extract by injection or by inhalation in adult asthmatics found no change in bronchial sensitivity after 12 weeks of injection of house-dust extract, but a significant decrease in the same parameter group treated by inhalation of dust extract. The clinical course was not described in this report. The total dose of extract in the injected group was substantially less than in Aas' study, but as noted above, comparisons between studies are difficult.

Another negative study of the effectiveness of immunotherapy with house dust extract was reported by the British Tuberculosis Association (Ref. 11). This cooperative trial of house dust extract included 33 asthmatic patients given injections of house dust extract for 15 weeks and then followed for 9 weeks thereafter. A comparable number of placebo injected asthmatic controls was similarly studied. There were no significant differences between the two groups in terms of symptom scores, days lost from work, medication scores, and tests of expiratory flow rate. However, the latter was done too infrequently to be of real value in assessment of effectiveness.

A trial of therapy for 16 weeks with aqueous extract of *D. pteronyssinus* in a small group (11 patients) of house dust and mite-sensitive patients with perennial asthma showed more improvement in the parameters studied, symptoms, and the need for mediciation compared with a group of 11 subjects treated with aqueous extract of human skin scales (Ref. 7).

Munro-Ashman et al. (Ref. 148) treated 52 patients with rhinitis and asthma, a clinical history of house dust allergy and a positive skin test to *D. farinae*. The treatment solution was prepared by adding *D. farinae* to house dust, then extracting with pyridine and suspending with alum. The course of treatment consisted of 9 to 10 injections, followed in some cases by maintenance injections. Four weeks after completion of the first course of treatment, 43 out of 52 patients were either asymptomatic or improved. Patients with asthma and those with rhinitis responded equally well. No control group was included in this study.

Smith and Pizarro (Ref. 105) treated 13 asthmatic children (mean age 13.4 years) with injections of house dust extract from Beecham Research Laboratories. The maximum dose was 0.8 mL of a 25-percent w/v aqueous extract and the course was 15 weeks long. Six of the patients reported improvement; seven were not improved. Of 17 other patients given *D. pteronyssinus* extract with a maximum dose of 0.01 percent w/v, 0.8 mL, only 7 reported improvement.

Taylor et al. (Ref. 149) carried out a double-blind placebo controlled trial of a house dust extract fortified with mite antigen. The subjects were 42 children with severe intermittent or chronic asthma, symptoms suggestive of house dust allergy and positive skin tests to both house dust and mite extracts. Each child received 10 weekly injections, beginning with 6 PNU and increasing to a maximum of 250 PNU in the active treatment group; the placebo group received injections of the diluent. The patients were assessed during and at the end of the course on the basis of height and weight, respiratory function, and chest examination. No difference between the two groups was shown. One criticism of this study is that the treatment dose may have been too small. Interestingly, the number of reactions (local or generalized reactions and/or wheezing within 8 hours; or worsening of respiratory function) was the same in both groups.

Warner and Price (Ref. 150) discussed some of the shortcomings of a study reported by Jaddie et al. (Ref. 144). They criticized the selection of patients, the conduct of the trial, the lack of definition of asthma or demonstration of bronchial lability, the failure to describe the method of recording symptoms and treatment and the choice of pulmonary function tests. (The same criticisms could be made about most of the studies the Panel has reviewed.) They state: "Trials of treatment of bronchial asthma are always difficult because of the heterogeneity and intermittent nature of the disease. Therefore, careful selection and assessment of patients are necessary if reasonable conclusions are to be drawn on the efficacy of any therapeutic regimen" (Ref. 150).

In a recent editorial in the British Medical Journal (Ref. 123), it was pointed out that dust-sensitive patients selected for studies of the efficacy of immunotherapy for asthma should have sensitivity to the offending allergen as the prime cause of their asthma; and the quality of the extract and optimal dose regimen should be carefully chosen. The editor also points out that immunotherapy always carries a risk, even though anaphylactic reactions are rare.

The Panel could find only one substantive study of the immunologic effects of house dust immunotherapy. May et al. (Ref. 66) showed that when house dust extract was administered according to "customary" dosage schedules (mean total dose over a 21-month period = 146,000 PNU) that only 3 of 21 subjects developed a significant increase in antigen-binding activity of their serum. In 5 of 21 subjects, there was a moderate increase in leukocyte cell sensitivity during the course of the injection treatment. However, of three subjects given "intensive" injection therapy, two had significant increases in antigen-binding activity in their serum. Subject A received 230,000 PNU in 6½ months; subject B received 30,000 PNU in 6½ months; and Subject C received 625,000 PNU in 3 months. Subject B developed an eight-fold increase, and Subject C developed a thirty-six-fold increase in serum antigen-binding activity. Subject B's leukocyte cell sensitivity fluctuated considerably during the course of injection therapy, while in Subject C, leukocyte cell sensitivity increased during the early weeks of treatment, remained high, and then gradually decreased after the injections were discontinued.

9. *Conclusions.* House dust extracts are prepared from source materials which are mixtures of many different substances and which cannot be precisely defined. By their nature, they are not of constant composition. Nevertheless, there is adequate evidence that extracts labeled "house dust extract" do contain one or probably more allergenic substances. Animal danders, especially cat and dog dander, are frequently present in house dust and may contribute to its allergenicity depending upon the amount of each which is present in the source material. The extent to which mite species contribute allergens to house dust, particularly those extracts produced in this country, is still undetermined. At the present time, the quantity of mites and/or their products in the source materials is not controlled. These generalizations apply as well to the other constituents of house dust.

Allergy to house dust appears to be a common occurrence, especially when the prevalence estimate is based on skin test reactivity. This sensitivity is manifested clinically mainly as perennial rhinitis and/or asthma. Symptoms in house dust-sensitive

people are often induced or exacerbated in situations with high concentrations of airborne household dust. However, persistent and perennial symptoms which are unrelated to obvious allergen exposure may also occur in dust-sensitive people. Also, most dust-sensitive people are usually allergic to other common allergens and the relationship of their perennial symptoms to contact with allergen or with nonallergen triggering factors is often difficult to determine. In particular, the quantitative association that has been established between airborne pollen and hay fever symptoms has not yet been fully established for household dust and allergic symptoms.

The natural history of allergy to house dust has not been documented.

There is no standard of potency for house dust extracts. They are currently produced on a w/v or PNU basis. Extracts with equal w/v or PNU designations may differ in biologic activity by more than a thousandfold.

The chemical composition of house dust extracts has not been determined. They are known to contain multiple allergens as well as varying amounts of endotoxins. The possibility that there is a single or a group of unique house dust allergens is unlikely, but it has not been ruled out.

The safety of house dust extracts as used in diagnosis and therapy has not been studied systematically.

The specificity and sensitivity of these extracts for the diagnosis of IgE-mediated allergy to house dust allergens has not been established. It may not be possible to do so until standardized preparations are available.

The effectiveness of house dust extracts in the treatment of sensitivity to house dust has not been established. This question remains to be examined in a well-designed clinical trial using an extract of adequate and well-established potency.

10. *Recommendations for house dust extracts.* It is recommended that house dust extracts be placed in Category IIIA for skin test diagnosis and immunotherapy.

b. Recommendations for the collection, processing, and storage of source materials to be used in the manufacture of house dust extracts:

(1) *Collection.* Various environments are suitable for the collection of these source materials. The collector should maintain a record of the actual location from which each sample of source material was collected. The method of collection of the source material, for example, by vacuuming, should be approved by FDA.

(2) *Processing.* Upon receipt of the source material, it should be inspected by the manufacturer and should meet standards for this product established by FDA. When required, it should be seived upon receipt from the supplier to remove contaminating debris.

(3) *Storage.* The source material should be stored under conditions approved by FDA. Particular attention should be given to the temperature and humidity during storage, and to the duration of storage.

c. The manufacturer must indicate the general nature of the source on the label. If the dust is obtained from households with animal pets, the label should indicate this also. For example, "a mixture of mattress and carpet dust" or "house dust containing animal dander." Only extracts made from source materials obtained from houses or similar establishments (e.g., hotels) or their appurtenances should be labeled "house dust extract."

11. *Endo™ dust.* Endo™ Allergenic Extract Purified Dust Concentrate was licensed by Endo Laboratories, Inc., Subsidiary of E. I. duPont de Nemours and Company (Inc.), but the production was halted during 1979. It was labeled for diagnosis and desensitization of patients allergic to house dust. It is a glycerosaline solution of products extracted from the dust found on the material collected during the ginning of cotton.

According to information obtained from Endo Laboratories, the original Endo™ dust was derived from the extraction of old mattresses. In more recent times, lint garnet dust was substituted as the source material. After cotton is ginned, a garnet machine is used to separate the long fibers from the short and some combing and spinning also take place. In the course of this processing, a large amount of fine dust is generated. Thus dust is called lint garnet dust. It has been examined for the presence of mites and is said to contain them, but no quantiative information is available. Endo ™ dust is an acetone-precipatated material, which is further extracted with an organic solvent, dioxane, similar to the procedure described by Boatner et al. (Refs. 15 and 75).

In general, safety and effectiveness comments made above about house dust extracts apply to Endo™ dust.

Although its effectiveness and safety have not been established in well-controlled clinical studies, there are sufficient claims of effectiveness and lack of evidence of significant adverse reactions to warrant further study of these questions. Therefore, the Panel recommended that Endo™ Allergenic Extract Purified Dust Concentrate, Endo Laboratories, License No. 147, be placed in Category IIIA for skin test diagnosis and immunotherapy. Near the end of the Panel deliberations, product marketing was discontinued.

12. *Autogenous dust extracts.* Autogenous dust is dust which is collected from the home of the individual patient for use in diagnosis and/or treatment of his/her own allergy. Methods for collecting autogenous dust and for preparation of extracts from it are given in Reference 4.

In general, many of the comments made above about ordinary house dust extracts apply to autogenous dust extracts. In addition, given that each autogenous dust extract is intended for use only in the patient from whose house the raw material was obtained, then it is apparent that the effectiveness and safety for diagnosis and treatment of a given autogenous dust extract can never be established by an adequate clinical trial.

However, when a reference standard for house dust extract is established and acceptable in vitro methods can be applied to the analysis of house dust extract, then it should be possible for the manufacturer to compare each batch of autogenous dust extract against a reference preparation of house dust. In the meantime, the Panel recommendations are the same as for house dust extracts.

Alternatively, since autogenous dust extracts are intended for use only in a given patient, an individual autogenous dust extract may not have to be licensed as must other extracts, but rather may be made available on a physician's prescription following established good manufacturing practices.

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F. Insect Allergenic Extracts

Allergic reactions may occur as the result of insect stings, insect bites, or inhalation of insect scales, dust or emanations.

Insect stings from *Hymenoptera* such as the bee, wasp, yellow jacket, hornet, and fire ant are responsible for a significant number of anaphylactic reactions including approximately 40 fatalities yearly (Ref. 1). Clinically, the symptom complex is typical of anaphylaxis from any cause, with the reaction usually starting within minutes following the sting. Atopic individuals are slightly at greater risk; and prevalence studies indicate that more frequent reactions occur in persons under age 20, with a 2:1 male to female ratio (Refs. 2 through 5). These latter factors may be a reflection of exposure.

Other adverse reactions may follow insect stings. Large local swelling may begin at the sting site and spread to adjacent areas, often taking 5 to 7 days to resolve completely. Occasionally, such local reactions precede subsequent anaphylaxis. Other unusual reactions attributed to insect stings include serum

sickness, renal disease, and a variety of neurological manifestations.

Reactions due to biting insects are less common and usually of a localized nature; anaphylaxis has rarely been reported. A large number of different insects have been implicated, although often there are only one to two case reports describing these reactions. Included in this group are insects such as fleas, mosquitos, and deerflies.

Inhalant allergic reactions due to inhalation of insect scales, dust, or enmanations are well documented. These are usually due to either localized environmental problems as in the case of the caddis fly or to unusual occupational exposure, e.g., beekeepers. The symptoms are typical of inhalant allergy and include rhinitis, conjunctivitis, and asthma.

Extracts relating to the following insects or insect substances were reviewed by the Panel:

1. STINGING INSECTS—ORDER *HYMENTOPTERA.*

a. Winged *hymenoptera:* bee, wasp, yellow jacket, hornet.
(1) Whole body extracts.
(2) Venom, bee.
b. Fire ant.
2. BITING INSECTS.
Order *Siphonaptera.*
a. Flea.
Order *Diptera.*
b. Mosquito.
c. Deerfly.
d. Blackfly.
e. Sandfly.
Order *Hemiptera.*
f. Bedbug.
g. Kissing bug.
d. INHALANT ALLERGY DUE TO INSECTS.
Class *Hexapoda.*
Order *Trichoptera.*
a. Caddis Fly.
Order *Ephemeroptera.*
b. May Fly.
Order *Homoptera.*
c. Aphid.
Leafhoppr.
Cicadas.
Order *Hymenoptera.*
d. Honeybee.
Order *Lepidoptera.*
e. Moth.
f. Butterfly.
Order *Coleoptera.*
g. Bean weevil.
h. Beetle.
Order *Diptera.*
i. House fly.
j. Screw worm.
k. Mushroom fly.
Order *Orthoptera.*
l. Cockroach.
m. Locust.
Class *Arachnida.*
Order *Aranea.*
Spider.
Class *Crustacea.*
Order *Isopoda.*
Sowbugs.
Order *Branchiopoda.*
n. Daphania (Water Flea).
o. Miscellaneous.

Insect Extracts for Insect Venom Anaphylaxis

1. *Stinging Insects.*—a. *Winged Hymenoptera (Bees, Wasps, Yellow Jackets, Hornets).*— (1) *Introduction.* The extracts which have been used for many years for diagnosis and therapy of individuals with insect venom hypersensitivity are whole body extracts prepared by extracting the crushed or mashed whose insect bodies. The origin of the preparation of whole body extracts rests with observations in the 1930's suggesting that the antigen responsible for allergic reactions is present throughout the whole insect body as well as in the venom (Refs. 6 and 7). While most clinical observations suggested that allergic patients who received treatment with whole body extracts had less reactions after subsequent stings, there has been growing dissatisfaction with the diagnostic and therapeutic results. As skin test diagnostic agents, whole body extracts have been found to be unreliable. Increasing numbers of treatment failures have been reported (see below).

Over the past 15 years, the potency of whole body extracts has been reexamined. Immunological studies by Shulman et al. (Ref. 8) indicated that there is a "tissue specific" antigen present in venom which is not found throughout the insect body. Studies in humans of the potency of whole body extracts using skin tests, histamine release assays, radioallergosorbent tests (RAST), and antibody response have shown that these extracts lack significant amounts of venom antigen(s).

Pioneer studies of Loveless (Ref. 9) suggested that pure venom was the appropriate antigen for diagnosis and therapy. This observation has been confirmed by more definitive studies in the past 5 years. At the beginning of the Panel review, one company (Center Laboratories) was licensed for bee venom for diagnostic use only. During the review, two companies were licensed for honeybee and vespid venoms for use as diagnostic and as therapeutic allergens.

(2) *Safety.* Unusual reactions, primarily involving the neurological and vascular systems, have been attributed to insect stings because of a temporal relationship. Such reactions mentioned in various references include serum sickness, acute glomerulonephritis, nephrosis, encephalitis, and Guillain-Barre' syndrome (Ref. 14). There is no reported increased incidence or awareness of such reactions in individuals such as beekeepers or patients treated with bee venom. However, it is also conceivable that had such reations occurred, the relationship to bee venom inoculations may not have been appreciated. Continued surveillance for these reactions in patients receiving venom for diagnosis or therapy is recommended.

There are two case reports suggesting that therapy with whole body extracts can lead to sensitization by nonvenom proteins. In the first report (Ref. 15), the patient developed joint pains and fever 24 to 48 hours after whole body extract injections. Histamine-release studies showed the presence of IgE antibodies reacting with whole body protein. There was no reaction with venom. In this report, other patients receiving whole body extract therapy were found to have elevated titers of whole body specific IgE, without any evident adverse reactions to these injections. Patients not receiving whole body extract thereapy did not have elevated whole body specific IgE.

In the second report (Ref. 16), a patient receiving whole body extract therapy had several typical systemic reactions after injections. His serum was found to contain whole-body-specific IgE, but no venom-specific IgE. These data suggested that he was sensitized by whole-body therapy.

(3) *Standardization.* Weight/volume and PNU are the usual potency standards for whole body extracts. It is doubtful that these parameters reflect the potency of an extract presuming that whole body extracts can be produced which retain venom allergenic and antigenic properties. Future measurements of potency must reflect venom or venom fraction content when used for insect sting allergy.

Limited data suggest that various whole body extracts may differ in potency. Sobotka (Ref. 10) reported differences in histamine release from leukocytes of allergic individuals using three different whole body insect extracts. In addition, differences were noted in direct skin tests of individuals with these three different extracts. Condemi reported that a large number of extracts were screened prior to choosing the one potent material used for their studies (Ref. 11).

Studies using RAST inhibition have shown definite differences in potency between three different whole body

extracts (Ref. 12). However, as compared to bee venom, none of these extracts had significant potency.

Bee venom has been standardized on a weight/volume basis using the absolute weight of lyophilized bee venom. As noted (Ref. 7), this may not be an accurate method of standardization. Skin test concentrations of 1 microgram per mL or less usually distinguish normal from control individuals. Nonspecific reactions may occur with venom concentrations of 10 micorgrams per mL or higher.

There has been one study comparing different bee venoms from various sources by chemical and biological assays. Measurements included nitrogen analysis, mouse toxicity tests, hyaluronidase content, and antigenicity as measured by the reaction with antibee venom rabbit sera. These studies showed that honeybee venoms from various sources were not identical and showed considerable variation (Ref. 13). This study suggests it may be necessary to standardize bee venom on some other basis than actual dry weight.

Hyaluronidase and phospholipase assays are required on each batch of bee venom licensed in 1979. No levels were set initially on phospholipase content. Hyaluronidase content levels were set, but may be changed as new assay methods are established.

(4) *Antigenic or allergenic relationships (specificity).* The order *Hymenoptera* of the class *Insecta* has two super families, *Apoidea* and *vespoidea.* The honeybee and bumblebee are the most important *Apoidea.* There are numerous species of *Vespoidea* of which the wasps, hornets, and yellow jackets are the most important.

Insect-sensitive patients may react to one specific insect or may be sensitive to several. For example, the distribution of bee, yellow jacket, and hornet venom-specific IgE antibodies, measured by RAST, in serum of 99 insect-sensitive patients is shown in Figure 1 (Ref. 17).

Studies using histamine release have shown similar differences in the specificity of patient sensitivity (Ref. 10).

It is likely that patients reacting to honey bee and vespid venoms have distinct specific IgE antibodies. In the case of reactions to two vespid venoms, such as yellow jacket and hornet venoms, it is not clear whether this is the result of cross antigencity or whether there are distinct antigenic components in each vespid.

(5) *Effectiveness for diagnosis*—(i) *Skin tests.*

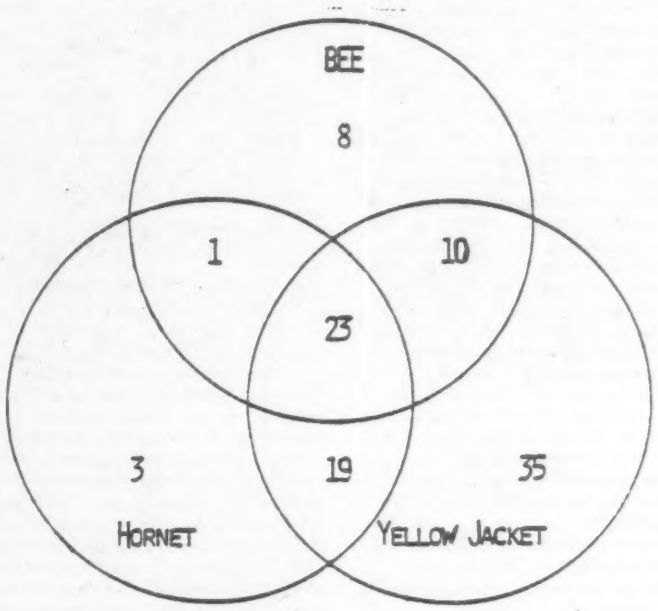

Figure 1 (Adapted from Ref. 17)
Distribution of specific IgE antibodies to bee, yellow jacket, and hornet venom in the serum of 99 insect-allergic patients.

(*a*) *Discrimination of the allergic from the nonallergic individual.* The validity of whole body extracts as diagnostic agents has been seriously questioned. Studies have been done comparing test results in discrimination of insect allergic individuals from insect nonallergic individuals. The following major studies seem most pertinent:

(*b*) *Studies comparing allergic patients and nonallergic controls.* Schwartz (Ref. 18) performed tests with varying dilutions of mixed whole body extracts on three groups of patients, insect allergic individuals, atopic noninsect allergic patients, and nonallergic individuals attending a venereal disease clinic. Tests were done with extracts in dilutions of 1:100, 1:1,000, and 1:10,000. The extract was obtained from the Allergy Laboratories of Oklahoma City. A positive test was one which reacted with a 10 mm wheal. There was no difference between the three groups in the results of skin tests with this material.

Sokotka et al., (Ref. 10) tested 13 insect allergic patients and 12 normal control patients with whole body extracts. They concluded that, while there is a tendency for the allergic patients to respond at lower extract concentrations, the overlap between the groups was so great as to make these materials of little diagnostic utility.

Further studies by this group (Ref. 19) testing 20 control and 20 insect allergic patients reached similar conclusions, that whole body extract failed to distinguish controls from patients. In contrast, in this study the use of insect venoms did distinguish the controls from allergic individuals.

In a double blind study, Zeleznick et al. (Ref. 20) studied the skin test reactivity of dialyzed hymenoptera venoms and whole body extracts. Venoms and whole body extracts of honeybee, yellow jacket, yellow hornet, white faced hornet and wasp were used. Most of the sensitive individuals had skin test reactions greater than the diluent control at concentrations of one microgram per mL or less of bee venom. Skin tests with whole body extracts prepared by Center Laboratories did not

produce a consistent differentiation between sensitive and nonsensitive individuals. All antigens were lyophilized and were reconstituted monthly with fresh dilutions prepared from the concentrated solution.

Extensive studies of hymenoptera venom skin tests were done on 30 patients with a history of anaphylactic reactions after a sting and on 30 control subjects (Ref. 21). The patients all had positive basophil histamine release to one or more venoms on challenge with specific venoms used for skin testing (honeybee, yellow jacket, white faced hornet, yellow hornet and polistes). At 0.1 microgram of venom per mL and at 1.0 microgram of venom per mL, 75 percent and 100 percent respectively, of the sensitive patients had a positive skin test. There was a significant ($p<0.001$) correlation between skin test and histamine release results. Of the 150 skin tests in control patients, only one was positive.

Center Laboratories was licensed in 1972 to manufacture bee venom for diagnostic skin testing. The clinical data initially submitted by Center Laboratories with their license application fails to clearly differentiate insect allergic patients from controls (Ref. 99). A total of 10 insect allergic and three nonallergic individuals were tested with bee venom from two sources. Results of these tests do not separate the two groups. In their product review information submission, skin test data on 26 patients with insect allergy are described. All but one patient reacted to bee venom in concentrations ranging from $1:10^3$ to $1:10^6$. The three control patients noted above, also reacted to venom in concentrations of $1:10^4$, $1:10^4$, and $1:10^6$. The Center Laboratories' bee venom for intradermal testing is a 1:1,000,000 ($1:10^6$) concentration. This would identify only five of the "allergic" patients and one of the control patients (Ref. 22).

Barr (Ref. 23) studied skin test reactions in 110 insect allergic individuals and 112 control group individuals. Hollister-Stier whole body extracts were used in dilutions of 1:10, 1:1,000 and 1:10,000. Insect allergic individuals generally showed more reactivity but there was considerable overlap. The only significant difference occurred at the 1:10,000 testing level at which nine positive reactions were found in allergic individuals and none in the nonallergic individual group.

Yocum et al. (Ref. 11) used Hollister-Stier mixed insect whole body extract. In this study, skin tests did distinguish fairly well between 46 insect allergic individuals and 21 control individuals.

(c) Testing of allergic individuals. Barr (Ref. 25) tested 249 insect allergic individuals with varying concentrations of mixed whole body extract. He reported that nine individuals reacted to 1:10,000 dilution, 101 to 1:1,000 and 139 to 1:100. No control studies were reported. However, only 7.6 percent of these individuals when tested with each of the specific insect extracts had a skin test reaction more positive with the specific insect identified as causing their reaction.

Gaillard et al. (Ref. 26) tested 124 patients who had experienced severe systemic reactions or large local reactions lasting several days. They used varying concentrations of four individual whole body extracts. They reported that only 60 percent had positive tests. No controls were done.

Mueller (Ref. 27) concluded that 85 percent of 55 patients with stinging insect allergy do have positive skin test reactions. He reported the occurrence of fairly exquisite skin test sensitivity in some individuals. There was no testing of control individuals in this series and no mention is made of what constitutes a nonspecific reaction.

Commenting upon this problem, Lichtenstein et al. (Ref. 28) stated "the diagnosis of anaphylactic sensitivity to hymenoptera except by history is currently impossible." This was prior to the availability of venoms for skin testing.

(d) Testing of nonallergic individuals. Bernton and Brown (Ref. 24) did intradermal testing of 200 normal individuals with varying concentrations of whole body honey bee extract. They concluded that about ⅗ of "normal" persons have skin reactions with this material.

(e) Degree of skin test sensitivity as related to clinical reaction. Mueller (Ref. 27) suggested that the more severe the clinical reaction, the greater is the skin test sensitivity to whole body extracts. Yocum (Ref. 11) similarly found a correlation between severity of whole body extract skin test reaction and stinging insect reaction. Terr and McLean (Ref. 29) studying whole body extracts in 26 patients with insect allergy concluded: "We have been impressed that as a general rule the degree of skin reactivity as determined by skin test titration seems to bear no relationship to the intensity of the clinical reaction to the insect sting."

(ii) *Conjunctival tests.* Kahn and Schwartz (Ref. 30) compared whole body extract conjunctival and skin tests in groups of insect allergic individuals and two control groups, atopic patients and nonatopic patients. They concluded that the skin test did not differentiate between these groups, but conjunctival tests did. Sixty percent of 52 insect allergic patients had positive conjunctival tests while only 8 percent of control patients had positive tests. They used a 1:10 whole body extract for conjunctival testing.

(iii) *Passive transfer tests.* Brown and Bernton (Ref. 31) did passive transfer tests with serum from 16 insect allergic individuals. They reported a positive test to at least one insect with all sera. Whole body extracts of individual insects were used for these studies.

(iv) *Histamine release from leukocytes.* There are two studies in the literature of particular significance studying histamine release from leukocytes of insect allergic individuals.

Sobotka et al. (Ref. 10) described the use of venoms causing histamine release. Six patients were studied all of whom released histamine with the addition of venom to white cells. Two of these six showed some release with the use of whole body extract, but the amont of histamine release was considerably lower than that found with venom.

Yocum et al. (Ref. 11) used only whole body extract and did not compare histamine release with venom. They found whole body extract was able to release significant amounts of histamine from leukocytes of sensitive individuals. Allergic individuals were clearly differentiated from controls. Histamine release and skin sensitivity were related.

(v) *RAST.* In one study, elevated levels of bee venom-specific IgE were found in the serum of 30 untreated bee-sensitive individuals. Fourteen of these patients also had elevated levels of IgE antibody reacting with whole body extract, generally in proportion to those of bee venom, but at lower levels (Ref. 12). The whole body extract was prepared in the laboratory.

RAST inhibition studies using discs coupled with bee venom and whole body extract showed three commercial whole body extracts to have generally little potency, but also to vary considerably in the degree of this potency (Ref. 32).

(6) *Effectiveness for immunotherapy*—(i) *Immunological studies.* Analysis of response to therapy using newly developed immunological parameters is presently a major area of investigation in several centers. The major reports are summarized as follows. Yocum (Ref. 11) reported that several patients treated with whole body insect extracts did develop "blocking" antibodies in their sera

capable of neutralizing histamine release (antigen-neutralizing activity).

Brown and Bernton (Ref. 33) retested individuals from 3 to 12 years after the original workup. They reported that skin tests tend to decrease in intensity. Of 100 patients, 57 percent had decreased skin test sensitivity, 32 percent were unchanged, and 11 percent increased in sensitivity. An obvious problem in the study is the unknown relationship of the activity of the extracts used for initial and subsequent testing.

Lichtenstein et al. (Ref. 28) reported the development of blocking antibodies capable of neutralizing histamine release. These antibodies developed following the use of pure bee venom for immunotherapy. In a large group of patients treated with whole body extract no blocking antibody activity could be determined. Bee venom was used as the challenging antigen.

Sequential serum samples from sensitive individuals have been analyzed for venom-specific IgE antibody titers (Ref. 34). RAST titers decreased in almost all individuals regardless of whether whole body extract injection therapy was administered or not. The decrease in the IgE antibody appeared to be a reflection of time rather than any specific immunotherapy with whole body extracts. In addition, levels of total antibodies (primarily IgG) reacting with bee venom were measured. Allergic individuals, both treated and untreated, had very low levels comparable to those found in controls. Much higher levels were noted in beekeepers. These studies suggested that whole body extracts were immunologically ineffective.

Studies by Sobotka et al. also showed stimulation of IgG antibody titers by venom therapy, but no stimulation by whole body extract or placebo therapy (Ref. 35).

(ii) *Clinical studies.* Numerous clinical studies have been done which would generally attest to the efficacy of whole body insect therapy. A number of these studies are summarized in a review of the literature by Barr (Ref. 36). The most complete study was by the Insect Committee of the American Academy of Allergy (Ref. 37), which contained "untreated" patients. The Insect Committee study is summarized in Table I.

TABLE I.—RESPONSE OF PATIENTS TO SUBSEQUENT INSECT STINGS

	Total patients	Same	Better	Worse
Desensitized (Treatment continuing)	569	19 (3.3%)	546 (96.0%)	4 (0.7%)
Desensitized (Treatment stopped)	470	31 (6.6%)	418 (88.7%)	21 (4.7%)
Not Desensitized	345	73 (21.2%)	225 (65.2%)	47 (13.6%)

The study by the Insect Committee suggested that over 95 percent of patients are better when restung if they have had whole body extract immunotherapy. However, approximately 65 percent of individuals had a similar response without receiving immunotherapy. Important factors which may influence the reaction to a subsequent sting in a previously sensitive patient and not accounted for in this study include: (1) Identification of the insect responsible for the initial and subsequent stings; (2) use of medication by the patient at the time of the sting, before the reaction ensures; (3) possible loss of patient sensitivity due to time alone; (4) development of IgG-type blocking antibodies as the result of the first sting.

There are a large number of other studies of the clinical response to whole body extract immunotherapy. Tuft and Torsney (Ref. 38) using alum-precipitated extracts reported that 6 of 23 patients when restung had no trouble.

Gaillard (Ref. 26) gave repository whole body extract treatment to 124 patients. Twenty-seven were restung and did not have systemic reactions.

As noted above, a more extensive summary of literature may be found in the literature by Barr. These results reflect the data noted above.

There are two reports (Refs. 28 and 39) of the failure of whole body extract therapy to provide immunity. Patients were subsequently successfully treated with pure bee venom. In addition, there is a report by Torsney (Ref. 40) of several individuals who died following insect stings despite having received treatment with whole body extracts.

In a recently reported single blind study using venom, whole body extract, and placebo, Hunt et al. (Ref. 41) reported the results after a 6-week course of therapy followed by challenge with venom. Three groups of patients were matched on the basis of skin tests and histamine-release sensitivity to venoms as well as by pretreatment IgG antibody levels and were randomly assigned treatment regimens. After immunotherapy the patients were challenged by injection with increasing doses of venom, and tolerating that, were stung by the culprit insect under carefully nomitored conditions. Only 1 of the venom-treated patients had a reaction to a sting, but 7 of the first 11 whole-body-extract treated patients challenged and 7 of the first 12 patients on placebo had immediate systemic reactions as a result of the sting. The study was then stopped since the difference in treatment outcome was highly significant. There was no statistical difference between placebo and whole-body extract. It should be noted that the whole-body extract dose was given over a 6-week period. This study suggested that whole-body extract was ineffective in providing immunity, while venom was highly effective.

(7) *Summary.* (i) Whole-body insect extracts have questionable usefulness for diagnosis of anaphylactic sensitivity to envenomation by stinging insects. These extracts clearly do not identify all or even the majority of insect-sting-allergic individuals. In all probability, venom antigens are present in negligible quantities in many, if not most, of these extracts.

(ii) Clinical studies are only suggestive of beneficial effect of treatment with whole-body extracts. Control studies have been limited, but in one single-blind study with carefully selected sensitive individuals, whole body extracts were therapeutically ineffective. Immunological studies have cast serious doubt upon the effectiveness of whole body extracts. Properly standardized venom should be the treatment of choice for these patients and is now commercially available.

(iii) Properly standardized pure venom appears to be the appropriate allergen for both diagnosis and therapy. In view of the reported differences in different bee venom preparations, some standard of potency, such as the hyaluronidase or phospholipase A content, is necessary.

(iv) Patients at risk for anaplylaxis should also depend upon the availability of emergency medication, including injectable epinephrine, and should be educated regarding means of insect avoidance.

(8) *Recommendations.* It is recommended that for stinging insect anaphylaxis, whole body winged *Hymenoptera* insect extracts be placed in Category IIIB for skin test diagnosis and immunotherapy. Standardized venom extracts should be placed in Category I for skin test diagnosis. Honeybee venom for diagnostic use licensed to Center Laboratories should be placed in Category IIIA, pending its meeting potency requirements and

further testing to substantiate clinical effectiveness and stability throughout the dating period. Honeybee, wasp, hornet, and yellow jacket venoms were licensed to two companies during the Panel review.

b. *Fire ant.* (1) *Introduction.* The fire ant is in the *Hymenoptera* order, belonging to the super family *Formicedae.* Two species of imported fire ants, *Solenopsis richteri* and *Solenopsis invicta,* are responsible for the majority of allergic reactions which occur from the sting of the fire ant. This insect is found in 13 Southern States, particularly in the Gulf coast area. Fire ant venom differs considerably from other *Hymenoptera* venom. It consists primarily of a suspension of insoluble alkaloids. Fire ant sensitivity usually does not imply sensitivity to other *Hymenoptera.* (Refs. 42 through 46).

(2) *Standardization.* Weight/volume and PNU are usually available standards of potency applied to the whole-body fire ant extracts. Alkaloids in fire ant venom have been isolated and synthesized. As yet, no chemical standard of potency is available.

(3) *Effectiveness for skin test diagnosis.* James et al. (Ref. 42) tested 18 patients who had had anaphylactic reactions to fire ants and 13 control individuals. The extracts used were a mixed fire ant whole-body extract and whole body extracts of *S. invicta* and *S. richteri.* These extracts were obtained from Greer Laboratories. Of 13 control patients, only 2 patients reacted at a 1:1,000 dilution of whole body extracts or extracts of specific fire ants. One control patient reacted at a 1:100 concentration, and 10 control individuals failed to react at all. Of the 14 patients tested with the mixed fire ant extract, 4 reacted to a 1:1,000, 5 to 1:10,000, and 5 to 1:100,000 dilutions. All 18 patients were tested with the individual extracts of *S. invicta* and *S. richteri.* In 4 individuals, these tests were negative. Six reacted at a 1:1,000 dilution, and the remaining eight reacted at higher dilutions of each of these extracts.

Lockey (Ref. 43) used a commercial extract of *S. richteri* for testing of 4 patients and 2 control groups. The source of the extract was not indicated. The four patients had positive scratch test reactions to the following amounts of the extract, 0.0005 PNU, 0.005 PNU, 0.05 PNU, and 0.5 PNU, respectively. One group of seven control patients consisted of nonallergenic individuals who had not had any reactions to other stinging insects. In this group, 4 patients had entirely negative skin test reactions, and 3 patients reacted at 250 and 500 PNU, respectively. A second control group consisted of individuals who had reactions to other stinging insects. Of these 6 patients, 1 patient failed to react to the fire ant extract. Five patients had positive reactions with the amount of materials needed to elicit the reaction ranging from 0.5 PNU to 500 PNU.

Rhoades et al. (Ref. 44) used a Greer Laboratory fire ant extract for testing of 34 patients who had allergic reactions following fire ant stings. Positive scratch tests were obtained in 15 patients, and positive intradermal tests were obtained in 20. One patient reportedly gave a negative rection. There was no control group for comparable testing. Of note was the fact that two patients did have systemic reactions following testing.

Triplett (Ref. 45) tested 17 patients who had had reactions from fire ants. In 2 individuals the tests were negative. Fifteen patients were positive at 1:1,000 or greater dilutions of fire ant extract. The fire ant extract was obtained from Hollister-Stier Laboratories. There was no control group.

The presence of specific IgE antibodies in the serum of fire-ant-sensitive indivudals was confirmed by passive transfer tests in two individuals (Ref. 42) and by positive RAST results in another group of patients (Ref. 46).

(4) *Effectiveness of immunotherapy.* Rhoades (Ref. 44) treated 39 patients with fire ant extracts. Ten patients were restung after receiving therapy for more than 3 months. There was one systemic reaction, and the other nine patients had local reactions only. There was no control group of patients who were not treated. The authors did mention that of 49 patients they had seen who had had systemic reactions from fire ants, 6 also had had other previous systemic reactions.

Triplett (Ref. 45) treated 18 patients with fire ant extract. Eight patients were restung with no reactions. Of note is the fact that four of these patients were restung while on treatment. Duration of treatment had been 3, 4, 8, and 23 months. The other four patients were stung following completion of 2 years of treatment. These restings occurred at 2 months, 2 years, 4 years, and 6 years, respectively, following completion of the 2 years of therapy.

(5) *Recommendations.* Whole body fire ant extracts appear to be reliable skin test antigens for the diagnosis of fire ant sting sensitivity.

Limited observations suggest that fire ant extract may be effective in the treatment of fire-ant-sensitive individuals. Observations of a control group of untreated individuals are lacking. It is possible that a patient's sensitivity may disappear as a result of time. In addition, corraborative immunologial studies are not available. It is recommended that whole body fire ant extracts be placed in Category I for skin test diagnosis and in Category IIIA for immunotherapy.

2. *Insect extracts for insect bite allergy.* There are only sporadic reports concerning allergic reactions due to most biting insects. Evaluation of biting insect extracts for diagnosis and therapy therefore must be based upon relatively meager information. In some instances in this section, data and recommendations will be generalized for biting insects as a group.

a. *Fleas (Order Siphonaptera)*—(1) *Effectiveness for skin test diagnosis.* A major study of flea extract was carried out by Feingold and Benjamini (Ref. 47). They prepared extracts from the cat flea, *Ctenocephalides felis,* by a variety of techniques. The extract prepared from whole cat fleas in aqueous solution was used for testing of a number of individuals. Two hundred and sixty-nine patients were tested. One hundred and three failed to react to intradermal testing with this extract. One hundred and sixty-six patients did react. Of these, 8 had an immediate reaction only, 53 had immediate and delayed reactions, and 105 had delayed reactions only. Passive transfer studies were not performed.

(2) *Effectiveness for immunotherapy.* Thirty-one individuals were given injection treatment with cat flea extracts (Ref. 47). All of these patients had positive immediate skin test reactions. The dose of extract for immunotherapy ranged up to a 1:50 concentration of the extract. Injections were given from 5 to 25 months. All patients were rechallenged by actual biting with the flea. In no case was the response to challenge improved over the original challenge done prior to the onset of immunotherapy. All challenge responses were the same or worse.

McIvor and Cherney (Ref. 48) used a flea extract prepared from the dog flea *(Ctenocephlides canis)* and the human flea *(Pulex irritans).* Skin testing data were not given. Sixty-seven patients were treated with this extract. Approximately 6 injections of a 1:5,000 dilution were given. The authors claim that following this type of treatment there was less intense and smaller size reactions following flea bites and that some patients responded after the first injection. The authors also stated that some patients indicated that fleas no longer were attracted to them following this treatment.

Hatoff (Ref. 49) used a mixed flea extract prepared from dog, cat and human fleas. No skin tests were done.

One hundred and twenty-nine infants and children were treated with a course of 15 injections. The author claimed that 78 percent of the patients were benefited, 5 percent had a questionable response, and 17 percent had no response. It is not clear how these patients were evaluated or whether they were really challenged with a subsequent bite.

(3) *Recommendations.* The reactions from flea bites are primarily large local reactions. Many of these reactions are delayed in onset as is the reaction found from testing with flea extracts (Ref. 47). There is no present documentation that reactions to flea bites have an IgE pathogenesis. The validity of flea extracts as diagnostic agents has not yet been established.

As noted above, there is some discrepancy in the results of studies with flea extracts as therapeutic agents. The best study (Ref. 47) failed to show that flea extracts are effective therapeutic agents. The Panel found no reports of immunological studies performed with this model. It is recommended that flea extracts be placed in Category IIIA for skin test diagnosis and in Category IIIB for immunotherapy.

b. *Mosquito (Order Diptera).* The role of allergy has primarily been studied in patients who develop delayed large local reactions following mosquito bites. Many of these reactions include vesicles, induration and even a development of some necrosis. Patients studied have not had anaphylactic type reactions.

(1) *Effectiveness for skin test diagnosis.* Rockwell (Ref. 50) studied a variety of extracts prepared from parts of mosquitos and different mosquitos. Essentially similar skin test reactions occurred with the extracts prepared from whole bodies as well as various parts including salivary glands, abdomen, and legs and wings.

Fifty-seven individuals were tested with bites of the mosquito, *Aedes aegypti,* and extracts of the mosquito. Patients developed immediate reactions and reactions some 24 hours later. There was a good correlation between the immediate reaction from the bite and the reaction elicited by a 1:10,000 dilution of the extract. This was not true for late reactions as more reactions occurred from the extract than from the bite.

Six patients who had large local reactions as described above were then studied. These patients showed immediate skin test reactions to lesser concentrations of mosquito extract than those found in the other control patients noted above. Reactions were found at 1:100,000 and 1:1,000,000 dilution of the extract. Passive transfer studies were attempted with the serum from 1 patient. Only 1 of 10 recipients showed a positive reaction. Further details were not given.

Benson (Ref. 51) reported four individuals who developed the same type of large local reactions as noted above. The mosquito extract used was *Aedes vexans.* His first patient had a positive immediate scratch test reaction from the concentrated extract. intradermal tests were positive at a 1:500 dilution. Both tests resulted in local reactions lasting 24 hours. Passive transfer tests gave "varying results." No controls were noted for the skin test with these mosquito extracts although in the discussion section Benson did claim that other individuals were tested. Two other sensitive individuals were tested and reacted in a similar manner. In subsequent seasons they had no further difficulty.

(2) *Effectiveness of immunotherapy.* Three patients were given immunotherapy starting at a 1:10,000,000 dilution of extract (Ref. 50). Injections were given every 3 to 5 days to a maximum tolerated dose (no details given). Two patients were followed for two summers, and one patient was followed for one summer. All patients reported less severe reactions, but did have significant local reactions persisting. There were no details concerning the control group not given injection treatment. One individual was treated with 6 injections of mosquito extract and developed delayed wheals 24 hours later at all injection sites (Ref. 51). Benson stated from the time of her first injection that she had lost her sensitivity. It is not clear how carefully controlled these observations were.

In a subsequent paper (Ref. 52), Benson extended these observations with a few more patients. He concluded that injection treatments were successful. These observations appear to be uncontrolled.

Brown et al. (Ref. 53) described an Arthus-like reaction occurring following a mosquito bite. No information is given concerning skin testing. The passive transfer test done with the serum of this individual gave conflicting results. Desensitization was attempted without benefit.

(3) *Recommendations.* Mosquito extracts used for disagnostic testing may have some value in confirming the delayed local reactions which some individuals have had following mosquito bites. An IgE pathogenesis for this type of reaction has not been established. There is no clear documentation that mosquito extracts are effective in the treatment of this type of reaction. It is recommended that mosquito extracts be placed in Category IIIA for skin test diagnosis and in Category IIIB for immunotherapy.

c. *Deerfly (Order Diptera).* Mease (Ref. 54) reported one case of an individual who developed large local reactions following deerfly bites. Extracts of deerfly were prepared. Tests done on two control individuals were negative. The patient reacted with a 1-centimeter wheal. The patient was given a series of injections for about 10 weeks and then treated in the subsequent year with a similar series of approximately 10 injections. Subsequently, he had no trouble following deerfly bites. It is not apparent whether he was actually challenged by a deerfly bite during this period of time.

Wilbur and Evans (Ref. 55) reported three patients with systemic reactions following deerfly bites. Two patients had wheezing and urticaria; one patient developed generalized anaphylaxis. All three patients had immediate positive intradermal skin tests to deerfly extract diluted 1:100,000. Tests on control patients were not reported. Passive transfer tests were positive with sera from all 3 patients; the titers were 30, 90, and 270. Histamine-release from leukocytes following deerfly extract challenge was positive in two patients. Immunotherapy was adminstered with deerfly extract. Two patients were bitten by deerflies 6 and 8 months later with "less reaction." Passive transfer titers diminished in all three patients, and histamine release reactivity decreased in the two patients.

It is recommended that deerfly extract be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

d. *Black Fly (Order Diptera).* Black fly bites commonly cause local skin reactions, which often last several days and may be pruritic or painful. There is one report describing the pathology of skin reactions following black fly bites (Ref. 56). In this report there are no data concerning the use of black fly extracts for either diagnosis or treatment.

It is recommended that black fly extracts be placed in Category IIIB.

e. *Sandfly (Order Diptera).* Arean and Fox reported skin test reactions from the bite of a sandfly (Ref. 57). One case report was given in which the patient developed large bullous lesions at the site of the sandfly bites. Lesions are well described. An immediate wheal reaction occurred first followed eventually by development of the bullaes. Skin tests with the extract resulted in the formation of papules within 24 hours.

Other control individuals were not tested. There is no information regarding treatment.

It is recommended that sandfly extracts be placed in Category IIIB.

f. *Bedbugs (Order Hemiptera).* Churchill (Ref. 58) reported one individual who developed generalized hives and edema apparently due to bedbug bites. No details were given regarding skin testing or treatment.

There is one report of anaphylaxis due to bedbugs (Ref. 59). No data are presented concerning the use of extracts for diagnosis or treatment.

There is one abstract by Sternberg (Ref. 60) reporting one individual who has asthma as a result of bedbug sensitivity. He had immediate skin test reactions to bedbug extract, and his serum also had definite reagins. This individual improved once the bedbugs were removed and apparently had no further difficulties. Skin tests with extracts of other common inhalants were negative. Skin tests of 60 patients with hayfever and asthma failed to reveal any reactions.

It is recommended that extracts of bedbugs be placed in Category IIIA for skin tests diagnosis and in Category IIIB for immunotherapy.

g. *Kissing Bug (Order Hemiptera).* Nichols and Green (Ref. 61) reported a number of individuals who developed large local reactions following the bite of the kissing bug, *(Triatoma protracta.)* Two individuals also developed generalized anaphylaxis. Extracts were prepared. Twelve individuals were tested. Immediate skin test reactions were found in all individuals. In nonallergic individuals immediate reactions were not found, but the number tested was not given.

In a recent study (Ref. 62), four persons bitten by *Triatoma protracta* were evaluated. The bites were single or multiple, painless, and occurred during sleep. Reactions ranged from generalized urticaria and angioedema to hypotension. Skin tests using whole body extracts of *T. protracta* produced immediate wheal and flare reactivity in sensitive patients. Histamine release studies using leukocytes from these patients demonstrated greater than 50 percent histamine release to intact *T. protracta* whole body extracts but no significant histamine release by control leukocytes. For certain individuals, dialyzed whole body extract preparations induced slightly to markedly less histamine release in comparison with undialyzed extracts.

It is recommended that kissing bug extract be placed in Category I for skin test diagnosis and Catetory IIIA for immunotherapy.

3. *Insect extracts for insect inhalant allergy.* Limited data relating to inhalant sensitivity to insects other than the Caddis Fly are available for review. Therefore, as in the section for biting insects, some data and recommendations will be generalized for the group.

a. *Caddis Fly (Class Hexapoda)*—(1) *Introduction.* The caddis fly has been well established as a cause of inhalant allergy. Its life cycle and habitat have been thoroughly described. It is primarily present in the Great Lakes area and, in particular, is a major problem along the Niagara River (Refs. 63 through 65).

(2) *Standardization.* Weight/volume and PNU are usual potency standards. Fractionation studies of caddis fly extract have suggested that the active allergen is a peptide of glycoprotein (Refs. 66 and 67). Positive skin tests were elicited in the skin of sensitive individuals. Analysis of this fraction has not been done as a method of establishing potency of extracts.

(3) *Antigenic or allergenic relationships (specificity).* Using the in vivo reagin neutralization method (Ref. 68), Parlato concluded that "the caddis fly antibody is similar to that of the butterfly and of the moth."

Langlois et al. (Ref. 69) studied the cross reaction of caddis fly with other insects including cricket, grasshopper, moth, and butterfly by tanned cell hemagglutination and gel diffusion experiments. They concluded that cricket and caddis fly had a strong degree of cross reactivity, and there was some antigenic relationship between the other insects and caddis fly.

(4) *Effectiveness for skin test diagnosis*—(i) *Skin tests.* Direct skin tests with caddis fly extracts have been used for the diagnosis of caddis fly sensitivity (Refs. 63 and 64, 70 and 71).

There are two reports of large studies of caddis fly extract skin testing. Parlato (Ref. 64) tested 162 patients and found positive reactions in 14.

Osgood (Ref. 70) tested 623 patients with 236 patients having negative reactions, 172 patients with slight reactions, 141 patients with moderate reactions and 74 patients with marked or greater reactions. The relationship between the place of residence (exposure) and the incidence of positive tests was evaluated. Twenty-two of 37 patients (60 percent) had moderate or marked test reactions where the patients were heavily exposed. With moderate-to-light exposure, 99 to 279 patients (35 percent) reacted similarly and in patients with little or no exposure, 31 of 142 patients (22 percent) reacted. The results were interpreted as showing a definite decrease in the occurrence of stronger skin test reactions with the increase in distance of residence from the known area of concentration of the flies. Osgood suggested that a patient who develops skin sensitivity has been exposed at some time to caddis fly or to some other insect which is related antigenically to the caddis fly.

Experience in the Niagara River area clearly confirms that testing with caddis fly extracts is very useful in identifying clinically sensitive patients; patients who are clinically sensitive have positive skin test reactions, and positive reactions of a moderate degree do occur occasionally in individuals without a history of exposure in accordance with Osgood's observations.

(ii) *Conjunctival tests.* Positive conjunctival tests have been described in patients with clinical caddis fly sensitivity (Ref. 64).

(iii) *Passive transfer tests.* Serum reagins reacting with caddis fly extract have been demonstrated by P-K testing (Refs. 64, 68, and 71).

(5) *Effectiveness and safety for immunotherapy*—(i) *Clinical studies.* Parlato (Ref. 63) reported one case of successful immunotherapy, associated with diminished skin and eye sensitivity.

Osgood (Ref. 70) treated 57 patients with caddis fly extract. The maintenance perennial dose of caddis fly extract ranged from 500 to 10,000 units every 4 weeks. The duration of treatment ranged from 9 months to over 17 years. He reported "good" results with 15 of 20 patients in whom caddis fly allergy was a major cause of symptoms with "fair" results in 4 of the other patients. "Good" results were reported in 21 patients and "fair" results in 10 patients in the group of 37 patients for which caddis fly allergy was a minor component.

(ii) *Immunological studies.* Langlois et al. (Ref. 72) examined serum from untreated and treated (immunotherapy) caddis fly sensitive patients for presence of hemagglutinating antibody. Nine of 31 untreated patients had positive hemagglutination results compared with 15 of 24 treated patients.

(iii) *Safety.* Local and systemic reactions due to immunotherapy with caddis fly extracts do occur. Osgood (Ref. 70) believes such reactions occur in about the same frequency as that seen from pollen immunotherapy.

(6) *Critique.* Caddis fly extracts are useful diagnostic skin testing agents for the confirmation of inhalant allergy due to caddis fly exposure. Limited clinical study and clinical impression suggest that immunotherapy with caddis fly

extracts may be effective in alleviating allergic symptoms due to caddis fly exposure.

(7) *Recommendations.* It is recommended that caddis fly extract be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

b. *May Fly (Class Hexopoda, Order Ephemcroptera)*—(1) *Effectiveness for skin test diagnosis.* The major study of May fly sensitivity has been done by Figley (Ref. 73) who evaluated the role of the May fly in causing respiratory allergies in the Toledo area. Twelve hundred and eighty-four patients with seasonal asthma and hayfever were tested with May fly extract. Ninety-five (7.4 percent) had significantly positive reactions. Forty of the 95 were clinically sensitive, and all had fairly marked skin test reactions. Twenty of these 40 reacted only to May fly extract and had corresponding clinical sensitivity. The other 20 reacted to ragweed as well as May fly. All 40 patients were treated with "satisfactory" results. Passive transfer studies were always positive when done. Specific numbers were not given. The other 55 patients with positive skin tests also had reagins demonstrated by passive transfer. It is not clear how many sera were actually tested. In addition, inhalation tests were also positive. These latter patients were not treated as they did not live in areas in which they were exposed to the May fly.

Further studies concerning May fly sensitivity were carried out by Parlato (Ref. 74). He also demonstrated significantly positive skin tests reactions to May fly extract in exposed individuals and believed May fly extract was helpful as a therapeutic agent. Positive P-K tests were also elicited.

These studies suggest that May fly extracts are useful for the diagnosis of inhalant May fly sensitivity.

(2) *Effectiveness for immunotherapy.* Control studies of therapy and studies of the immunological response of therapy have not been reported. Other uncontrolled results from immunotherapy are mentioned above.

(3) *Recommendations.* It is recommended that May fly extract be placed in Category I for skin test diagnosis and in Category IIIA for immunotherapy.

c. *Aphid (Class Hexapoda, Order Homoptera).* There is one report on the study of the aphid as an insect allergen (Ref. 75). Gaillard tested 121 patients who had seasonal allergic rhinitis and asthma with an extract prepared from the aphid. There was one systemic reaction to testing. Seventy-five patients had significantly positive skin tests, and 59 of these 75 had clinical symptoms which possibly correlated with aphid exposure. Control patients were not tested. The majority of these patients also reacted to other common airborne allergens. Fifteen of 17 sera obtained from these patients contained reagins detected by passive transfer studies. In addition, *in vivo* neutralization studies in patients with both ragweed and aphid sensitivity confirmed the specificity of this passive transfer reaction.

It is recommended that aphid extract be placed in Category I for skin test diagnosis and in Category IIIA for immunotherapy.

d. *Bee (Order Hymenoptera).* Ellis and Ahrens (Ref. 76) reported two cases of individuals who developed inhalant sensitivity as a result of exposure to bee dust. In the first individual the inhalant sensitivity followed an anaphylactic reaction to a sting. The second individual was a beekeeper who was commonly around bee hives. Extracts were prepared from whole bee as well as a number of bee parts. For the most part, all these extracts elicited positive skin tests. Passive transfer tests were also positive with serum from both individuals. One individual also had a positive challenge test with an extract of bee sprayed into a room. He was subsequently hyposensitized with "excellent results."

It is recommended that whole body bee extract be placed in Category I for skin test diagnosis of inhalant bee "dust" sensitivity and in Category IIIA for immunotherapy of inhalant bee "dust" sensitivity.

e. *Moths (Order Lepidoptera).* Urbach and Gottlieb (Ref. 77) reported one individual who apparently had an inhalant sensitivity following exposure to moths. Scratch tests with moth extracts were positive and were negative in two controls. Passive transfer tests were not carried out. Injection therapy was given with apparently satisfactory results, but at the same time the moths were eliminated from the house.

The moth extract may be a useful diagnostic agent. Further control studies are certainly necessary to document its effectiveness. As a therapeutic agent, its effectiveness was not established.

It is recommended that moth extract be placed in Category IIIA for skin test diagnosis and in Category IIIB for immunotherapy.

f. *Butterfly (Order Lepidoptera).* Parlato (Ref. 78) considered the possible allergenicity of scales and hairs of the butterfly and moth and their relationship to the caddis fly. Extracts of the butterfly and moth were prepared. Six caddis fly-sensitive patients were tested; four had strongly positive intradermal test reactions; and two patients were moderately positive. As controls, 10 pollen sensitive patients and 5 nonallergic individuals were tested, and all were negative. One P–K test was attempted and was positive.

In a second paper (Ref. 79) the relationship of the butterfly, moth and caddis fly was examined. In vivo reagin neutralization studies were done with the sera of caddis fly-sensitive patients. Positive P–K tests were found with all 3 insect extracts. Following exhaustion of the P–K site by each of the insect extracts (caddis fly, moth, butterfly), there was no reaction elicited by subsequent challenge with the other insect extracts. Thus it appeared from these experiments that butterfly, moth and caddis fly shared an allergen.

These experiments suggest the possibility of inhalant allergy due to butterfly and moth scales and hairs. The clinical relevance of these observations has not been established.

The antigenic relationship between various insects was also studied, using rabbit antisera and gel precipitation and hemagglutination analyses (Ref. 80). Common antigenicity between the cricket, grasshopper, moth, butterfly and caddis fly was demonstrated. The moth and butterfly showed the greatest number of common antigens. The relevance of this type of approach, using antibodies directed at whole insect antigens, to human inhalant allergy, is not known.

It is recommended that butterfly extracts be placed in Category IIIB.

g. *Mexican Bean Weevil.* Wittich (Ref. 82) reported two individuals who were working as sorters in a seed house who developed typical allergic respiratory problems as a result of exposure to peas and beans infested with the Mexican bean weevil. Both patients had rhinitis, and one patient had asthma. These symptoms occurred only while working in the seed house. Skin testing with a variety of extracts revealed very definite reactions to an extract prepared from the Mexican bean weevil. Tests with other types of common inhalants and peas, beans and corn were entirely negative. Three control patients had negative skin tests. Serum from both sensitive individuals had reagins demonstrated by a positive passive transfer test. Both patients were given injection therapy with a bean weevil extract, and the author reports a good response in both individuals. Both were able to continue work and apparently became much less symptomatic.

The bean weevil commonly infests peas and beans. Bean weevils have

small hair-like scales which commonly rub off. Apparently the inhalation of these scales is responsible for allergy symptomatology.

It is recommended that extracts of Mexican bean weevils be placed in Category IIIA for skin test diagnosis and for immunotherapy.

h. *Beetles (Order Coleoptera).* Sheldon and Johnston (Ref. 81) reported a case of nasal allergy and asthma due to beetle emanations. Immediate positive skin tests were present with a beetle extract. Passive transfer tests were positive as was a nasal challenge test. Controls "in adequate numbers" were negative. This study suggested beetle extract might be effective in the diagnosis of inhalant beetle sensitivity.

The Panel recommends that identified beetle extracts be placed in Category I for skin test diagnosis and in Category IIIB for immunotherapy.

i. *House Fly (Order Diptera).* Jamieson (Ref. 83) reported one individual who apparently had inhalant sensitivity to house flies, causing sneezing. Scratch tests were performed with flies' wings, rubbed into the area resulting in a fairly marked reaction and also a delayed local reaction. A similar reaction occurred when the tests were repeated on one occasion. Passive transfer studies were positive on several occasions. Nasal and conjunctival tests were also positive. This study suggests that house fly extracts may be effective diagnostic agents for house fly inhalant sensitivity.

It is recommended that extract of house fly be placed in Category I for skin test diagnosis and Category IIIB for immunotherapy.

j. *Screwworm (Order Diptera).* There was only one study of inhalant allergy due to excessive exposure to the screwworm fly (Ref. 84). In this one study extracts were useful diagnostic agents. It is not clear how many control individuals were also tested. There were no therapeutic studies.

It is recommended that extracts of screwworm fly be placed in Category IIIA for skin test diagnosis and Category IIIB for immunotherapy.

k. *Mushroom Fly.* There are two reports of the mushroom fly as an inhalant cause for bronchial asthma. Mushroom flies appear in swarms in spring and fall months in areas of mushroom farms. Larvae get into mushroom beds from the horse manure pile when spring and fall plantings occur, eat out the stems and cups of the growing mushrooms, leave the mushroom houses through doors and ventilators, and descend on the neighborhood in clouds. Inhalation of the emanations or parts of these flies can cause wheezing. These flies are prevalent in southeast Pennsylvania, but they could be found anywhere nushrooms grow. The use of DDT has cut down considerably upon their incidence.

Truitt (Ref. 85) prepared extracts of the mushroom fly in Coca's solution, 0.56 mg nitrogen per cc. Intradermal testing was done with 0.005 mg nitrogen per cc. The results of testing patients in an endemic mushroom fly area, Westchester, Pennsylvania, showed 50 out of 316 patients reacting. Nine of the patients who reacted exhibited symptoms. There were no reactions in 50 patients tested in a nonendemic area in the city of Philadelphia.

Truitt described five individuals with asthma associated with fly exposure. All had positive intradermal tests. Passive transfer tests were attempted with the sera of two individuals and were positive on both occasions. He also reported treatment with "good results." No other specific data are given.

Kern (Ref. 86) reported one individual who developed asthma following exposure to mushroom fly. He had a typical story of symptoms upon exposure to the fly. Skin tests revealed a very definite immediate skin test reaction, and at the same time he had a mild systemic reaction from the testing. control subjects were negative when tested. The patient's serum did have reagins. Injection treatment with mushroom fly extract apparently was successful in alleviating his difficulties.

It is recommended that mushroom fly extract be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

l. *Cockroach (Order Orthoptera).* Bernton and Brown (Ref. 87) tested 253 normal individuals with cockroach extract and found approximately 7.5 percent positive reactions. Of 114 other individuals who had an inhalant allergic disease, 28 percent had positive reactions to cockroach extract. Passive transfer tests were positive in 22 of 23 sera from this latter group of patients. These studies apparently established the validity of cockroach extract as a diagnostic agent in determining the presence of specific reagins reacting with cockroach. The clinical significance of these studies is not clear. Sensitivity might have been acquired through ingestion or inhalation. There are no studies of therapy.

There are a number of other studies of the use of cockroach antigen for diagnostic testing.

Bernton and Brown (Ref. 88) used an extract of the German cockroach, *Blattela germanica, Linnaeus,* 24 PNU per milliliter. In a group of 102 children attending an allergy clinic, 38 percent showed reactions to the cockroach antigen. Only 5 percent of 100 healthy individuals reacted similarly to intradermal testing. These authors also quoted two other studies: (a) Schulaner (Ref. 89) found that 40 percent of 95 allergic children reacted to cockroach skin testing; (b) Mendoza and Snyder (Ref. 90) found that 30 percent of 181 asthmatic children reacted.

Kang (Ref. 91) skin tested 22 asthmatic individuals. Sixteen had positive reactions with cockroach extract, and six had negative reactions. Of the 16 with positive skin tests, 14 had positive inhalation challenges, and two were negative. The six individuals with negative skin tests all had negative inhalation challenges. Appropriate controls were done with saline and unrelated antigens. Thirteen of the 14 patients with positive inhalation challenges also had late reactions. These late reactions could be inhibited with the use of cromolyn. Skin testing was done with a 1:20 weight/volume extract for prick testing and a 500 PNU/milliliter testing for intradermal testing.

Bernton and Brown (Ref. 92) tested patients in the allergy clinic of seven hospitals in New York City with a dialyzed residue of an extract of German cockroach, 0.4 PNU per mL. The patients were selected and tested routinely. A total of 755 patients were tested. Of these, 589 belonged to 4 ethnic groups (Puerto Rican, Negro, Italian, Jewish). There were 419 positive reactions to routine allergens and 170 negative reactions. There were 257 positive reactions to cockroach allergy and 332 negative reactions. Positive cockroach reactions in ethnic groups included 161 reactors in 272 patients of Puerto Rican descent (59 percent), 82 reactors among 173 persons of Negro descent (47 percent), 9 reactors among 53 persons of Italian descent (17 percent), and 5 reactors among 91 persons of Jewish descent (5 percent).

There were no studies found on the use of cockroach extract immunotherapy.

It is recommended that extract of cockroach be placed in Category I for skin test diagnosis and Category IIIB for immunotherapy.

m. *Locust.* Frankland (Ref. 93) discussed allergic respiratory problems in workers exposed to locusts in a laboratory. Extracts of several locusts were prepared. In all, he tested 34 workers exposed to locust in the laboratory. Eighteen had positive skin tests, and 4 of these 18 had symptoms. Reference was also made to 2 other symptomatic patients who were

exposed to locusts, thus a total of 6 symptomatic patients were reported. A positive passive transfer test was attempted with the serum of 1 patient and was positive. As a control, 71 other patients with grass hay fever were tested. Two had positive reactions to locust extracts, 7 were doubtful, and 62 were negative. Frankland also described desensitization in 1 patient. Results appeared to be successful, but specific data are lacking.

It is recommended that locust extract be placed in Category I for skin test diagnosis and in Category IIIB for immunotherapy.

n. *Water Flea.* Way (Ref. 94) reported one individual apparently sensitive to inhalation of the water flea, a small animal of the phylum *Arthropoda.* One of the common types of water flea is *Daphnia pulex.* Water fleas are commonly used as food for fish. The individual reported developed asthma at home. Investigation revealed he had a large number of fish, and he used Daphnia as fish food. Further investigation finally led to testing. He had strong skin test reactions to Daphnia extract, and his serum also contained reagins demonstrated by positive passive transfer. Discontinuation of exposure to Daphnia led to complete remission of all symptoms.

It is recommended that extract of water flea be placed in Category I for skin test diagnosis and in Category IIIB for immunotherapy.

o. *Miscellaneous Insects.* There are several studies evaluating skin tests with different insect extracts in individuals with inhalant allergic disease, primarily rhinitis and asthma (Refs. 95 through 98).

Hellreich (Ref. 95) tested 30 patients with perennial allergic rhinitis and asthma selected at random and 30 patients with asthma who were basically skin negative individuals with the following extracts: cockroach, ant pupa, cricket, daphnia, grasshopper, housefly, mousy grub, silk pupa, silk worm, and blister beetle. The number of patients reacting to each of these extracts were determined and it would appear that all extracts gave reactions at about equal percentage. (Roughly 33 to 40 percent of the patients.) No control patients were done. Passive transfer studies were done with sera from three individuals and two sera were positive with daphnia and one serum with ant.

Feinberg et al. (Ref. 96) tested 130 patients with nasal allergy and asthma with a variety of insect extract: May fly, silk cocoon, silk pupa, grasshopper, ant eggs, house fly, mosquito *(Aedes aegypti),* honey bee, daphnia (water flea), Mediterranean fruit fly, and melon fly. A significant number of positive skin tests were found. In patients with strongly positive tests, P–K tests were positive. The clinical relevance of these tests was not determined. The authors also claim good results of desensitization, although it is not clear how well the patients were really evaluated in this regard.

Perlman performed extensive skin tests with a large number of insect extracts (Refs. 97 and 98). In one series (Ref. 97), 252 consecutive patients were tested. About 50 percent reacted to at least one of the extracts. P–K tests were positive with selected sera.

Among the insect extracts eliciting positive reactions were (Ref. 98): spider, spider web; sowbug, daphnia, leaf hopper, aphid, black fly, earwig, moth, and deerfly. Data concerning the number of positive reactions for each extract in patients and a control group are not given. Demonstration of serum antibodies (P–K) for each of the insect extracts is also not presented.

These studies suggest that there may be IgE specific antibodies reacting with a variety of insect extracts. The purity of such extracts has not been determined, and thus the specificity of some of these reactions is still questionable. The clinical relevance of these reactions is also not known.

The literature about mite extracts is discussed with house dust extracts. Specific mite extracts are recommended to be placed in Category I for skin test diagnosis and Category IIIA for immunotherapy.

Therefore, the Panel recommends that the other marketed extracts of insects for which there is evidence of the insect causing allergic reactions be placed in Category IIIA for skin test diagnosis because of the potential for these extracts to react with IgE-specific antibodies in sensitized patients. These extracts should be placed in Category IIIB for immunotherapy because of a lack of evidence that the products are effecitve or safe. Where the Panel could find no information that a specific insect is responsible for an allergic reaction, the extract has been recommended to be placed in Category IIIB. Table II lists the generic recommendations for the licensed insect extracts reviewed by the Panel.

TABLE II.—INSECT EXTRACT RECOMMENDATIONS

Marketed extract	Literature references available	Recommended categories	
		Skin test diagnosis	Prophylactic immunotherapy
Aphid	Yes	I	IIIA.
Bedbugs	Yes	IIIA	IIIB.
Bee, Bumble	No	IIIB	IIIB.
Bee, honey	Yes	IIIB [1]	IIIB. [1]
Bee, honey	Yes	I [2]	IIIA [2].
Bee sweat	No	IIIB	IIIB.
Bee, venom	Yes	I	
Beetle blister	Yes [3]	I	IIIB.
Beetle, dermestid	Yes	I	IIIB.
Bettle, Japanese	Yes [3]	I	IIIB.
Beetle, ladybug	Yes [3]	I	IIIB.
Black-fly	Yes	IIIB	IIIB.
Box elder bugs	No	IIIB	IIIB.
Butterfly	Yes	IIIB	IIIB.
Caddis fly	Yes	I	IIIA.
Caterpillar	No	IIIB	IIIB.
Caterpillar (tent)	No	IIIB	IIIB.
Citrus mealy bugs	No	IIIB	IIIB.
Clear lake gnats	No	IIIB	IIIB.
Cricket	Yes	IIIA	IIIB.
Cicada/locust	Yes	IIIA	IIIB.
Cockroach	Yes	I	IIIB.
Cockroach, American.	Yes	I	IIIB.
Cockroach, German	Yes [3]	I	IIIB.
Cockroach, Oriental	Yes [3]	I	IIIB.
Cockroach, mixed	Yes	I	IIIB.
Daphnia	Yes	I	IIIB.
Deer fly	Yes	I	IIIA.
Fire ant	Yes	I	IIIA.
Flea	Yes	IIIA	IIIB.
Flea, dog	Yes [3]	IIIA	IIIB.
Flea, cat	Yes [3]	IIIA	IIIB.
Flea, mixed	Yes	IIIA	IIIB.
Flea, sand	Yes	IIIB	IIIB.
Flea, water (daphnia pulex).	Yes [3]	I	IIIB.
Fruit flies	Yes	IIIA	IIIB.
Gnat	No	IIIB	IIIB.
Gnat, black	No	IIIB	IIIB.
Grasshopper	Yes	IIIB	IIIB.
Hornet	Yes	IIIB	IIIB.
Hornet, bald face	Yes	IIIB	IIIB.
Hornet, black & yellow mix.	Yes	IIIB	IIIB.
Hornet, Japanese	Yes [3]	IIIB	IIIB.
Horsefly	No	IIIB	IIIB.
Horsefly/stable fly	No	IIIB	IIIB.
Housefly	Yes	I	IIIB.
Household insects	No	IIIB	IIIB.
Kissing bug	Yes	I	IIIA.
Leafhopper	Yes	IIIA	IIIB.
Locust	Yes	I	IIIB.
May fly	Yes	I	IIIA.
Mexican bean weevil.	Yes	IIIA	IIIA.
Mite (D. farinae)	Yes	I	IIIA.
Mosquito	Yes	IIIA	IIIB.
Mosquito mix	Yes	IIIA	IIIB.
Moth	Yes	IIIA	IIIB.
Moth/miller	Yes [3]	IIIA.	IIIB.
Mushroom fly	Yes	I	IIIA.
Sandfly	Yes	IIIB	IIIB.
Screwworm fly	Yes	IIIA	IIIB.
Sow bugs	Yes	IIIA	IIIB.
Spider	Yes	IIIA	IIIB.
Spider mix	Yes	IIIA	IIIB.
Stable flies	No	IIIB	IIIB.
Tick seeds	No	IIIB	IIIB.
Triatoma	Yes	I	IIIB.
Wasp	Yes	IIIB	IIIB.
Wasp mix	Yes	IIIB	IIIB.
Yellow jacket	Yes	IIIB	IIIB.
Stinging insect mix	Yes	IIIB	IIIB.

[1] For stinging insect anaphylaxis.
[2] For inhalant allergy to the insect body parts.
[3] References not specific for species.

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G. Food Allergenic Extracts

Adverse reactions to foods were recognized at the beginning of the recorded history of man. Our language is replete with expressions such as, "one man's meat is another man's poison," which indicates the widespread appreciation of the fact that ordinarily innocuous food may cause significant disease in susceptible individuals. The beginnings of allergy as a clinical science may be traced to the experiments of Prausnitz and Küstner (Ref. 1) on the nature of an active substance in haddock which caused hives when one of the investigators (Küstner) ate the fish. They found that the substance responsible for the adverse symptoms was a nondialysable, heat stable protein. The substance (as did an extract of cooked fish itself) elicited a wheal and flare reaction when scratched into Küstner's skin. Furthermore, they were able to show that Küstner's serum contained a transferable factor which conferred local sensitivity to haddock when injected intracutaneously into a non-fish sensitive individual.

A vast amount of largely descriptive literature on the diagnosis and treatment of food allergy has accumulated during the past 50 years. In few other conditions are diagnoses made with such variable standards as in food allergy. It has been proposed, for instance, that "food allergy" can cause a wide spectrum of symptoms other than those observed in the classical atopic disorders of hay fever, asthma, and urticaria (Ref. 3). The true incidence of food allergy is difficult to establish. Some physicians consider almost all symptoms allergic as long as they occur after ingestion of food. Others restrict

the use of the term "food allergy" to conditions in which an immunologic mechanism is demonstrable or strongly suspected. Adverse reactions with similar symptomatology without demonstrable immunological components are better classified as intolerances or idiosyncrasies, e.g., enzyme deficiencies, toxic effects of bacterial contamination of foods, and toxic factors intrinsic to the food itself or additives used in processing, to name a few.

The best defined allergic reactions to food are those mediated by IgE antibodies. Thus, anaphylactic type reactions to fish, egg white, nuts, peanuts, milk, and certain grains are well described, are easy to diagnose clinically and immunologically, and are universally accepted as allergic disorders. Dermatitis resulting from a cellular hypersensitivity caused by contact with foods occurs, but is less common. Although the standards for the investigation of food allergy have not been as rigid as today's standards for properly conducted clinical investigation of inhalant allergy, the specificity of food allergens in the causation of allergic disease has received considerable attention over the past 50 years.

1. *Specificity of food allergens.* It has been said that skin tests are unreliable for the diagnosis of food allergy. This holds true only if reactions are caused by antigens which differ substantially from the food from which they are derived or when food has induced the formation of antibodies other than IgE. IgE mediated reaction studies should be expected to meet the criteria which apply to the study of other atopic diseases. Preparing potent food extracts is difficult because of the perishable nature of foods and the presence of primary irritants, which are not easily removed. Furthermore, identification of the components of processed foods cannot always be assured. Patients may attribute their symptoms to food, but processed food may not even contain the food which its name implies, e.g., chocolate flavoring may replace cacao, and other processed products may contain active allergens not identified in the label of the food. These variables often greatly influence the patient's ability to identify the component of food which causes his symptoms.

Nevertheless, some investigators have overcome most of these problems and have shown that patients with atopy give skin reactions to food extracts more frequently than do normal controls (Refs. 4 and 5). Pearson (Ref. 6) in comparing the egg white skin test in 224 asthmatics with 103 normals found positive reactions in 18 percent and 1 percent, respectively. In doing a similar test for egg white on 200 allergic and 200 normal children, Fontana et al. (Ref. 7) reported 16 percent and 0 percent reactions, respectively. Additional tests by Fontana showed up to 45 percent reactions in the same groups of allergic patients, compared with 1 percent or less reactors among the normal individuals, to wheat, rye, codfish, cow's milk, lamb, and peanut. On the other hand, tests with strawberry, spinach, and "chocolate" were less discriminatory being 33 percent and 20 percent, 26 percent and 18 percent, 19 percent and 11 percent, respectively. The specificity of these three food extracts in this study is highly questionable, and these results suggest that the preparations used may contain a primary irritant. Hill (Ref. 8) studied 100 asthmatic children ages 3 to 12 with food extracts using the scratch method. Thirty-five children had one or more positive tests to food allergens. Sixty-five children failed to react. In those individuals having negative skin tests, there was no clinical evidence that asthma was caused by the ingestion of food.

2. *Food as a cause of allergic disease.* Atopic individuals react to food extracts in about the same manner in which they react to inhalant extracts and present the same basic problem, to establish a causal relationship between exposure and symptoms.

Allergenic extracts of food present different assessment problems than extracts of seasonal and environmental inhalant allergens. Allergies to multiple foods, more common in infants than in adults, might be atopic and followed, later on, by "classical" sensitization to inhalant allergens. Unlike sensitivities to inhalants (which one acquired, tend to persist through life) childhood allergies to foods often fade and only occasionally continue into adult life.

Yet, the established sensitivity to a single food, such as Prausnitz' sensitivity to haddock, is immunological. Judged objectively, it suggests that an early component of the immunological sequence, a macrophage perhaps, has mistaken the fish for a parasite and has mobilized the IgE-mast cell-eosinophil-dependent defense against it. The transitory nature of "atopy" which extends to foods makes it difficult to judge whether immunotherapy alters the natural history of, e.g., the milk-sensitive infant.

Prausnitz and Küstner's observations demonstrated that, against expectations, food, either intact or, at least, its intact antigenic components, could and did pentrate the gastrointestinal tract and elicit allergic reactions at distant sites. The initial observations have been confirmed by others, e.g., by Freedman (Ref. 11) and Walzer (Ref. 53). Even if foods were cleaved into individual peptides and amino acids within the gastrointestinal tract, individual amino acids can influence the synthesis of essential mediators which encourage or inhibit allergic reactions. If foods are absorbed intact or after incomplete cleavage in the gastrointestinal tract, several questions may be asked, such as: Are food and food products which penetrate the gastrointestinal barrier attached, like drugs, to carrier molecules which protect their premature breakdown and determine their ultimate destination? What is the evidence that abnormally absorbed food products can induce the formation of antibodies other than IgE? Some of these questions have been answered. Serum profiles of children show a rather surprising titer of precipitating antibodies to milk. Comparably few foods have been analyzed as carefully as milk; and for most foods, the allergenic component has not been identified.

3. *The "nonreaginic" allergies to food.* The major part of this discussion of food extracts covers those foods which are known to induce IgE-mediated reactions in susceptible individuals. Yet many discussions about the entire complex of "allergies" to foods are not limited to IgE-induced immunological illness (Refs. 3, 56 through 59, and 61). The terms "nonreaginic food allergy", "masked allergy," "allergic tension-fatigue syndrome", symptom "neutralizing" and "provocative" techniques, and the "type V" response might cover significant clinical events, but are not consistent with current classifications of allergic reactions (Ref. 60). These concepts should be evaluated by means of controlled research. It is possible that these are nonimmunological rections but no one can be sure. One cause of the uneasiness of both IgE-trained allergists and the "nonreaginic" groups has been the use of poorly defined material for clinical trials. It seems that the FDA might be of considerable help to investigators employing both concepts by insisting on adequate characterization of the extracts under study.

4. *IgE-mediated food allergies.* Hill (Ref. 8) in his study of 100 asthmatic children with one or more positive skin tests to food observed the effect of food ingestion in those children who had positive skin reactions. He reported:

a. In 24 children, asthma could be produced by a specific food which was usually recognized prior to any testing;

b. Altogether, there were 218 positive scratch tests. Forty-four appeared to be clinically significant in that ingestion of the food could cause asthma. Foods included in this group were egg white, fish, peanut, walnut, chocolate, tomato, spinach, orange, corn, and barley. There were 16 other cases in which food ingestion tests caused irritation about the mouth, urticaria, vomiting, or edema. These foods included asparagus, banana, egg white, fish, orange, peanut, spinach, and walnut.

c. One hundred fifty-eight positive food skin tests could not be correlated with clinical symptoms.

Adams (Ref. 9) and Chobat and Hurwitz (Ref. 10) found that about 20 percent of positive scratch tests to food in groups of allergic children were clinically significant. These results are similar to those found by Hill.

Freedman and Sellars (Ref. 11) tested 150 consecutive "allergic" children seen in consultation for an allergy evaluation. Almost all had typical allergic disease. Skin tests were done by the scratch method using commercial food extracts and "natural foods." There was a strong correlation between skin test reactions to nut, peanuts, fish, peas, and shellfish and an anaphylactic clinical response. In 30 instances there were 13 foods giving strongly positive reactions. In 21 of these 30, the reaction was associated with clinical sensitivity to the food. There were 107 positive skin reactions which were not of clinical significance.

May (Ref. 12) studied 38 children with chronic asthma in whom food hypersensitivity was incriminated in the history. Symptoms were evoked in a double-blind food challenge in 11 of 38 children and in 14 of 70 challenges. The symptoms were characteristic of immediate-type hypersensitivity reactions (primarily gastrointestinal). Peanut was responsible for eight reactions, egg for five and cow's milk for one. The feature which most successfully identified those having positive reactions in challenges was a significant wheel reaction in the skin test by puncture technique using an extract of 1:20 weight to volume concentration. No subject with clinically significant symptomatic hypersensitivity to food had a negative puncture test. Puncture tests were positive in only 10 of 56 instances of negative reactions in food challenges.

5. *Skin testing and detection of serum food specific IgE.* Golbert, Patterson, et al. (Ref. 13) reported studies of patients who had had systemic allergic reactions to ingested antigens. These reactions were all of acute anaphylactic type. Foods responsible for these reactions included pinto beans, halibut, rice, potato, brazil nut, shrimp, garbanzo bean (chick pea), tangerine, and milk. In almost all instances there was a positive skin test correlating with the positive histories, and when performed, the serological passive transfer test was positive. In addition, histamine release from leucocytes was positive in some patients. A patient allergic to brazil nut was also allergic to pistachio. A patient allergic to shrimp was also allergic to lobster.

Hoffman, Haddad et al. (Ref. 14) examined sera from patients with atopic eczema by the radioallergosorbent test (RAST). Twenty-five sera were examined with 18 different food antigens in the RAST procedure. Specific IgE antibodies were found reacting with the following foods: almond, chocolate, corn, codfish, egg white, organge, peanut, shrimp, tomato, walnut, milk, wheat, oat, rice, avocado, and cantalope. Comparison of the results of food RAST's with direct food skin tests and clinical symptoms were not made.

In two reports, Chua et al. (Refs. 15 and 16) studied the relationship of direct skin tests and RAST's in patients with suspected food allergy. In the first report, 86 patients were studied who were clinically sensitive to foods. Studies included passive sensitization of human and monkey lung, RAST, and direct prick tests. The results of prick testing and history correlated in 72 percent of instances. The results of the RAST and prick test correlated in 72 percent, while the RAST correlated with history in only 54 percent of instances. Passive sensitization of tissue was not as predictive. Specific serum antibodies and skin test reactions were found with peanut, egg, fish, and nuts. The fish included pickerel, halibut, and salmon.

In the second report more sera were analyzed and RAST was found to be positive less frequently (52 percent) than the prick test (70 percent) in the diagnosis of immediate type food allergy in clinically sensitive patients. Combining RAST and prick tests, 74 percent were positive.

Galent et al. (Ref. 17) studied patients with food sensitivity with a variety of techniques including direct skin tests, leucocyte histamine release and cytology in skin windows. In this study there were 15 patients with immediate reactions to foods. In most instances these patients had positive skin tests and evidence for circulating specific IgE antibodies. The foods implicated included egg, peanut, walnut, fish and milk.

6. *Specific food allergens.* There are over 140 vegetables, cereals, fruits, nuts, condiments, meats, seafoods, milk, and eggs which have been reported in clinical literature and proven to be allergens. Some of these have been studied chemically and biologically in great detail. The investigation of others has been limited to the testing of a few patients reporting clinical sensitivity to food. Among the foods intensively investigated are milk and codfish.

a. *Cow's milk.* Milk is a unique mammalian adaptation which provides infants with a complete natural food. Milk received by the human infant from its mother causes minimal, if any adverse effects. When a mother is unable to or will not nurse the infant, a variety of milk substitutes are available, the most common of which is cow's milk.

(1) *Composition of cow's milk.* The opalescent appearance of milk is due to the presence of micelles of the caseins, the principle proteins in milk. The micelles incorporate other milk constituents. Mature bovine milk is composed of caseins, the whey proteins (*a*-lactalbumin, *b*-lactoglobulin), iron binding proteins (lactoferrin, transferrin) and a protein of unknown function called lactolin. In addition, many enzymes, including lactoperoxidase, acid phosphatase, alkaline phosphatase, protease, xanthine oxidase, amylase, lipases, ribonucleases, lysozyme, and carbonic anhydrase are present but some are destroyed during pasteurization. Lipids including fat, phospholipids, sterols, carotenoids, and Vitamins A, D, and E are also found. The principal ions of milk are calcium, magnesium, sodium, potassium, phosphates, and citrates. In addition to the fat-soluble vitamins, other vitamins are present in varying quantities. There are also other nitrogenous compounds and trace elements. Thus, milk is a highly complex mixture of proteins, lipids, carbohydrates, and inorganic compounds.

The nomenclature for milk proteins has been controversial for many years, and much of the older literature is not consistent with newer publications causing confusion in the designation of various protein components.

(i) *Caseins.* Caseins have been fractionated into a number of components known as alpha caseins, beta caseins, and kappa caseins. There are many genetic variants of these proteins which are found in a concentration of about 25 grams per liter (g/L) in mature bovine milk.

(ii) *Whey proteins.* The two principal whey proteins of bovine milk are beta-

lactoglobulin and alpha-lactalbumin. Beta-lactoglobulin is found in a concentration of 3 g/L., and alpha-lactalbumin is 0.7 g/L. in mature cow's milk. There is no beta-lactoglobulin in human milk. In contrast to beta-lactoglubin, alpha-lactalbumin is known to be present in human milk.

(iii) *Iron-binding proteins.* The iron-binding proteins of milk are lactoferrin, which is a red colored protein that is specific to milk, apo-lactoferrin, the iron-free form of lactoferrin, and transferrin, which is identical to transferrin of serum. The green iron-binding enzyme of milk is known as lactoperoxidase and is one of the most abundant enzymes of milk. A protein called lactolin is found in small concentrations of bovine milk. Its biological function is unknown, but it is of interest that it is found to a much greater concentration in colostrum than in mature milk. Serum albumin in milk is identical to serum in the blood. As noted above, milk contains a wide variety of enzymes, some of which are secreted by the mammary gland and others appear to be of bacterial origin. Already noted to be the most abundant enzyme in milk is lactoperoxidase. Acid phosphatase, alkaline phosphatase, amylase, lactase, lysozyme, ribonuclease, and xanthine oxidase are also found in milk.

(iv) *Immunoglobulins.* The immunoglobulins of colostrum are secretory immunoglobulin A (SIgA), IgM and small amounts of IgG. In mature milk, the principal immunoglobulin is SIgA. In addition, isohemoglutinins belonging to the IgM class have also been reported to be present in milk. In nonhuman species such as the horse, pig, cow, and rodents, no placental transfer of immunoglobulin occurs, and the colostrum is the principal source of passively-acquired immunity in the species, and thus is critical for survival. In the rabbit, guinea pig, and man, transfer of immunoglobulins takes place transplacentally, and thus the specific antibody content of mother's milk has not been considered an important source of immunity in these species. Human milk possesses a significant antiviral activity and inhibits growth of mumps, influenza, herpes simplex, and several encephalitic viruses. The nature of this antiviral activity is unknown.

(2) *Adverse reactions to cow's milk.* Antibodies to milk proteins can be found in virtually 100 percent of individuals who drink milk if tests of appropriate sensitivity are used. There appears to be no relationship between serum antibody level and clinical milk sensitivity. On the other hand, there is a good correlation between in vivo and in vitro tests that measure specific IgE antibodies to the milk proteins and milk-induced clinical sensitivity of the immediate type following ingestion of milk. A good deal of effort has been extended toward the identification of the principal allergenic substances in cow's milk, and numerous attempts have been made to modify the allergenic properties of milk by heat or other treatments. The whey proteins have been implicated since the beginning of the century as the principal allergens in cow's milk. Much of the older work can be discounted on the basis of the impurity of the preparations used in the in vivo and in vitro tests. The most carefully done studies on the allergenicity of casein, alphalactalbumin, and beta-lactoglobulin have not revealed the importance of one particular protein over another in terms of its allergenicity. The studies of the effect of heat on cow's milk utilizing immunoelectrophoretic techniques have that the immunoglobulins are most sensitive to heat treatment, while beta-lactoglobulins and alpha-lactalbumin were altered little under the heating conditions used in the study. Goat milk has been recommended in the past as suitable for individuals who have cow milk sensitivity. However, recent studies have shown that caprid and bovine they proteins are closely related immunologically (Ref. 18).

Goldman et al. (Ref. 19) skin tested a group of normal, allergic (but not to milk) and milk-allergic children with four purified milk antigens: Casein, BSA, beta-lactoglobulin, and alpha-lactalbumin. Tests were done by both scratch and intrademal methods. Six of 102 normal subjects gave one-plus positive results. No more than one positive reaction was recorded in each of the six responders. Of the positive responders, 1 was in a group of 24 newborns, 2 were from a group of 38 infants 2 weeks to 12 months in age, and 3 were in a group of 40 children over 1 year.

In the allergic (but not allergic to milk) group, 21 of 31 (68 percent) had a positive skin test to one or more proteins. Seventeen of the 21 with a positive skin test were positive to two or more proteins. Of the 124 tests applied to this group (31 patients X 4 tests), 16 were positive to casein, 5 to alpha-lactalbumin, 15 to beta-lactoglobulin, and 15 to BSA. Forty reactions were graded one-plus, and 11 reactions were graded two-plus.

In the allergic-to-milk group, 50 of 85 (59 percent) had positive skin tests to one or more proteins. Thirty of 50 patients had a positive skin test to two or more proteins. Thirty-four were positive to casein, 22 to alpha-lactalbumin, 20 to beta-lactoglobulin, and 21 to bovine serum albumin. Twenty of the 97 tests were strongly positive.

Weakly-to-moderately-positive skin tests to purified milk proteins have little diagnostic significance because a group of allergic children who were not allergic to milk had a higher frequency (68 percent) of positive reactions than did the group allergic to milk (59 percent). Strongly positive skin tests to purified milk proteins were limited to milk-allergic children. These tests correlated well with oral challenge with the same protein.

Negative as well as positive skin test reactions to milk proteins occur in the milk-allergic patient, and neither are associated with any particular symptom, age of onset of hypersensitivity, severity of reaction, or other features of oral challenge reactions. False-positives and false-negatives were observed in both whole milk and with fractions.

There are a number of older studies in the literature using whole cow's milk and relatively impure (by today's standards) milk fractions. Skin tests with these extracts are of limited value in an individual case, but as suggested by Goldman (Ref. 19), a strongly positive skin test by the cutaneous technique correlates well with clinical milk sensitivity of the anaphylactic type.

b. *Vertebrate fish, Mollusca, and Crustacea.* Tuft and Blumstein (Ref. 20) prepared extracts of fish from different families all belonging to the subclasses *Teleostomi* and *Elasmobranchii.* Extracts included the following fish: shark, skate, sturgeon, carp, codfish, flounder, sole, shad, salmon, blue fish, rock bass, and yellow perch. Direct skin test, passive transfer test, and in vivo and in vitro reagin neutralization studies were done with six fish-sensitive individuals. Results of these studies indicated a common antigen among members of the fish family. There was a quantitative difference in the presence of this antigen among various species. Positive intradermal tests and the presence of specific reaginic antibody to all of the above fish could be demonstrated in the sera of the patients.

Tuft and Blumstein (Ref. 21) also studied the sera of six patients sensitive to *Crustacea* (lobster, shrimp, crab) and *Mollusca* (clams, oysters, scallops). Positive direct skin tests as well as specific antibodies in serum were found to all of these preparations. The authors concluded there is a common antigen among the *Mollusca* family. Among the *Crustacea,* all fractions are present in lobster. The crab fraction is present in

shrimp, and the crab does not contain lobster or shrimp fractions.

c. *Cod.* Allergy to vertebrate fish may be considered the prototype of IgE-mediated food allergy. Allergic reactions to fish are generally immediate and most commonly are manifest by the appearance of urticaria (most often angioedema) and asthma. Conjuctival, nasal, and gastrointestinal symptoms (vomiting, colic, and watery diarrhea) are commonly seen. Either raw or cooked fish may act as an ingestant and an inhalant allergen (Ref. 22). Küstner's fish allergy was unusual in that the allergen appeared to be found only in cooked, and not in raw, fish.

The fish that has received the most intensive study is cod *(Gadris callaris).* The diagnosis of allergy to cod is easily established because of the temporal relationship of ingestion or inhalation of cod to the appearance of eye, skin, respiratory, and gastrointestinal symptoms (Ref. 22). Reagins to cod may be regularly demonstrated by the passive transfer test, and cod-specific IgE antibodies may be demonstrated by the RAST test and by leucocyte histamine release.

The white muscle myogens of cod provide the source of the most potent material for preparation of diagnostic extracts. Myogens are the sarcoplasmal proteins as contrasted with the myofibrillar proteins (acetomyosin, myosin, and actin). The conventional extraction procedure using saline or Coca's solution yields a potent extract (Ref. 23).

Myogens of fish are not represented among mammalian proteins. Their amino acid content and strongly acidic characteristics are different from those of human proteins, and as such are recognized as foreign.

A homogenous allergenic protein from cod designated "Allergen M" can be cleaved with trypsin, and the two polypeptide fragments isolated have been designated "TM_1" and "TM_2." Both were equally reactive by direct skin test, passive transfer, and RAST. The molecular weight for Allergen M is 15,000, for TM_1 8,500; and for TM_2 6,500. TM_1 represents the aminoterminal part of the molecule. Allergen M and fragment TM_1 have one residue of glucose. A carbohydrate moiety was found not to be necessary for the biological activity of fish antigens, which is contrary to what has been reported for other allergens. Allergen M in a concentration of 0.1 mg/mL elicites reactions corresponding to those elicited by histamine 1 mg/mL when both were used in puncture tests. Allergens M, TM_1, and TM_2 were shown to have qualitatively identical allergenic activity. This was shown by neutralization of sensitized sites with one of three fragments and challenge with the other two and also by lack of flareup of neutralized sites after the recipient ingested 200 grams of cooked cod. The RAST test, however, showed that the fragments do not appear to be an active as the whole extract (Ref. 24). Different commercial extracts from fish vary in protein content and immunological characteristics when compared on an equivalent mg/mL total protein basis (Ref. 25).

In one study, 61 children with asthma and/or urticaria caused by allergy to fish were tested with six species of fish, including cod, fresh water trout, and salmon (Ref. 22). Thirty-four reacted to all fish tried, and 27 showed distinct specificity. Other studies also indicate that there are common allergens and species-specific allergens in the fish family (Ref. 26). Thus, whole cod extracts and low-molecular-weight fragments were found to be potent and highly reliable diagnostic allergens.

A few cod-sensitive patients have undergone attempts at desensitization by oral or injected cod fish extract. The results have been of limited value at best, and the procedure was accompanied by a significant degree of adverse allergic reactions.

d. *Egg.* Chicken egg is one of the more common and allergenic foods causing IgE-medicated allergic reactions, including urticaria, gastrointestinal symptoms, anaphylaxis, and less commonly as rhinitis and asthma.

Eggs are most often ingested, but may be inhaled in the powdered form and may act as a simple contactant in highly allergic patients thus causing immediate dermal reaction or mucous membrane swelling. Exquisitely sensitive patients may react to minute amounts of egg proteins found in some vaccines, particularly yellow fever vaccine.

Physically, the egg can be divided into the white and the yolk. The yolk contains lipoproteins and a water-soluble fraction called livetin. The allergenicity of the yolk protein is less than the egg white protein.

The white, which is composed almost entirely of protein, contains the primary allergens. The major proteins are ovalbumin and ovomucoid. There are less important and less abundant proteins including lysozymes, ovomucin, flavoproteins, and others.

Ovalbumin is the most abundant protein in the egg and accounts for about 50 percent of the total solids. The sulfhydryl groups are unique to this protein and may account for its physical, chemical, and immunological behavior. Ovalbumin is coagulated at relatively low temperatures in the course of preparation for human consumption.

Some controversy exists as to the relative allergenic importance of the ovalbumin and the ovomucoid. Probably each may at times be the major allergen in egg-sensitive patients. It has been generally accepted that the ovalbumin is the major allergen that causes symptoms. This has been demonstrated with pure crystalline material (Ref. 27).

Positive skin test reactions in egg-allergic individuals correlate well with clinical symptoms observed following ingestion of egg. In vitro tests using RAST have confirmed the specificity of the allergen and the presence of IgE antibodies in subjects who give positive skin test reactions and who have strong clinical histories (Ref. 27).

Egg allergen is an important cause of clinical symptoms, and the extract should be available for skin testing. Although egg white provides the primary source of allergen and ovalbumin contains the major allergenic substance, ovomucoid appears to be an allergen in a minority of individuals. Thus, it may be of value to have egg white as well as ovalbumin and ovomucoid available for the investigation of patients in need of a precise diagnosis. For practical purposes, whole egg white should suffice as an allergen. In some individuals, however, a reaction to ovomucoid may be an indication that even cooked egg will be clinically allergenic.

e. *Soybean.* Duke (Ref. 28) studied one individual who worked in a soybean mill who was highly sensitive to inhalation and ingestion of soy. He had a direct positive skin test, and serum reagins were demonstrated by passive transfer testing. Duke also reported four other patients who worked in a soybean mill who had asthma and positive skin tests to soybean extract.

Mortimer (Ref. 29) reported an infant who developed anaphylaxis following soy ingestion. This child had a markedly positive skin test and also had serum reagins demonstrated approximately 2 years later.

Mortimer did direct skin tests with soybean extract on 220 allergic infants and children by scratch and intradermal methods. Approximately 26 percent of these patients had positive reactions. These observations suggest that in an allergic pediatric population there is a significant incidence of positive skin tests to soybean. However, correlation of positive skin tests with clinical manifestations of allergy was poor with only 7 percent of skin-test positive patients reporting clinical sensitivity.

f. *Fruits.* Tuft and Blumstein (Refs. 21 and 30) studies four patients who developed symptoms of mouth swelling and throat itching following ingestion of a variety of fruits. Positive skin tests were elicited as well as passive transfer tests, particularly with juices from the fruits. The authors claimed that commercial allergenic extracts were ineffective in eliciting these reactions. Following stewing or canning of the fruits, their extracts lacked potency, but retained potency when made from fresh-frozen fruits. Also, Seitz filtering caused a reduction in extract potency.

Among the food juices which elicited positive reactions were the following: Watermelon, honeydew, cantaloupe, pears, peaches, pineapple, grape, bananas, oranges, and apples.

In a subsequent study, Tuft and Blumstein (Refs. 31 and 20) demonstrated positive skin reactions to fresh peach extract with presence of reagins in the serum. The antigen was thermolabile and deteriorated very rapidly on storage.

(1) *Orange.* Bendersky and Lupas (Ref. 32) reported one individual who developed anaphylaxis following ingestion of orange juice. This individual had a positive skin test to fresh orange extract and specific reaginic antibodies in his serum demonstrated by passive transfer testing. Skin tests in a control population were negative. In addition, this patient had a negative reaction to a stock orange extract.

Williamson (Ref. 33) reported an individual who had clinical anaphylaxis after ingestion of two oranges. No immunological studies were performed.

(2) *Mango.* There are a number of case reports of allergic reactions following ingestion of mango. Rubin et al. (Ref. 34) and Dang and Bell (Ref. 35) reported cases of individuals who developed acute anaphylaxis following mango ingestion. In the report by Rubin et al. The patient had specific reagins demonstrated by passive transfer testing. Direct skin tests were not performed. There were no immunologic studies in the second case report.

(3) *Grape.* Brown (Ref. 39) reported an individual who developed symptoms of sneezing, rhinorrhea, coughing, wheezing, edema, and hives following ingestion of grape wine. Immediate skin test reactions were positive to grape. Passive transfer tests were markedly positive to grape, grape seek, and commercial grape juice. The patient was markedly improved by avoidance of grape products.

(4) *Banana.* Fries and Glazer (Ref. 40) described two individuals who had gastrointestinal symptoms characterized by nausea, vomiting, and abdominal pain following banana ingestion. One individual also developed local swelling and vesicles on his lips following contact with banana. Both individuals had strongly positive skin tests to banana extract. Passive transfer studies done with one individual's serum was strongly positive.

g. *Nuts.* Gillespie et al. (Ref. 44) used the RAST for detection of specific IgE antibodies reacting to nuts in 18 patients with a clinical history of nut sensitivity. Specific IgE antibodies were demonstrated. Passive transfer tests were also positive with the sera of four of the patients. The authors also prepared their own peanut and almond extract. Positive tests were obtained with peanut in the sera of five patients, almond in three patients, brazil nut in nine, black walnut in four, English walnut in three, pecan in two, and cashew in three patients.

h. *Vegetables*—(1) *Green Pea.* Malley et al. (Ref. 43) studied the allergens in green pea extract. They concluded that the most allergenic and antigenic fraction in green pea is associated with the albumin fraction.

Direct skin tests were done on 10 pea-sensitive patients and were positive with both the crude extract and the pea albumin fraction. There are no clinical details concerning sensitivity nor are there reports of similar testing on control individuals. Passive transfer tests were positive with the sera of several individuals. In addition, cross sensitivity with green bean, soybean and alfalfa was studid and there was evidence of a common allergen among these substances.

(2) *Potato.* There are several papers dealing with allergenic reactions due to potatoes. These involve reactions in individuals exposed particularly while peeling potatoes. Pearson (Ref. 36) interviewed 1,200 patients with asthma and found 29 with a history of asthma following peeling potatoes. He reproduced the asthma experimentally in 6 of 10 patients. Four patients in a total group of 29 were unable to eat cooked potatoes. The others tolerated cooked potatoes with no difficulty. Positive skin tests with fresh raw potato juice extract and commercial potato extract were found in some patients.

Nater and Zwartz (Ref. 37) reported a case of respiratory allergy due to inhalation of raw potato. This patient was able to eat cooked potatoes. Direct skin tests and passive transfer tests were positive with fresh potato extract and negative with cooked potato extract.

(3) *Tomato.* Bleumink et al. (Ref. 38) studied the allergen in tomato extract. Nine patients with atopic diseases were found who had strongly positive skin test reactions to tomato. All reacted to an active fraction isolated from tomato which was thought to be the potent allergen. The basic purpose of this paper was to isolate the allergen in tomato extract. At least three of the nine patients had clinical histories suggestive of tomato sensitivity. There were no control studies done by skin testing normal individuals. There were no passive transfer tests performed.

(4) *Vegetable gums.* There have been a number of papers describing allergic reactions to ingestion of vegetable gums. Gelfand (Ref. 41) reviewed the previous reports of vegetable gums causing allergic reactions particularly by inhalation, contact and ingestion. He reported on 10 patients with allergic problems due to ingestion of vegetable gums. All patients had positive skin reactions with three gums—karaya, tragacanth and arabic. In four patients passive transfer tests were done and were positive with all three gums. Ingestion experiments reproduced symptoms in five of the patients studied.

Brown and Crepea (Ref. 42) reported one individual who developed asthma and generalized urticaria following ingestion of gum tragacanth which was taken as part of a tablet. Immediate skin tests and a passive transfer test were positive.

(5) *Peanut.* Peanut is classified as a legume. Peanut is a potent food allergen and causes a wide variety of allergic symptoms, including: Urticaria, angioedema, gastrointestinal symptoms, and asthma in sensitive patients.

Because of biological relationships to other legumes, cross-reaction of peanut has been investigated. Gillespie (Ref. 44) found that pea did not significantly inhibit the peanut RAST. It was also shown that little, if any, antigenic cross-reactivity exists between peanut and Brazil nut.

Data submitted by Allergy Laboratories, Inc., Oklahoma City, Oklahoma, showed no positive skin test reactions to peanut extracts in 33 control patients and 17 percent positive skin test reactions in 97 allergic patients who were subsequently placed on immunotherapy with one or more extracts (Ref. 63).

Radioallergosorbent testing using peanut has been reported by a number of authors (Refs. 15 and 44 through 46). IgE antibody to antigens in peanuts can be demonstrated readily.

Because of the danger of serious reactions, caution is needed in testing patients with a high degree of sensitivity to peanut. Using only scratch or puncture tests minimizes the possibility

of serious systemic reactions if diagnostic testing is deemed necessary.

i. *Sesame seed.* Uvitsky (Ref. 47) reported one individual who developed acute angioedema of the lips, tongue and uvula which was related to ingestion of a sesame confection. Strong immediate skin test reactions were found with sesame seed extract. Passive transfer tests were also done and showed a positive direct test. The patient was challenged with sesame seed and developed an immediate systemic reaction. Tornsey (Ref. 48) studied three individuals in detail who had acute anaphylactic reactions following ingestion of sesame seeds. All patients had positive skin tests and specific IgE antibodies demonstrated by passive transfer testing. Direct skin tests done on 10 control patients were negative. In addition, Tornsey referred to two other reports in the literature describing similar reactions from sesame seeds.

7. *The preparation of food allergens.* The preparation of food allergenic extracts represents a critical factor in the controversy over the merits of the use of these extracts for clinical diagnosis. Allergens should be subjected to as little denaturation as possible and should be free of nonspecific irritants. As with other extracts the final product should be stable.

The extracts should be made from the edible portions of food or frozen foods at their usual stage of maturity. Some foods must be preserved from the Maillard reaction (nonenzymatic browning) (Ref. 49), or from alteration by continued action of intrinsic enzymes, which can be accomplished by blanching, by freezing, and by the use of reducing chemicals such as ascorbic acid or sodium formaldehyde sulfoxylate (Ref. 50).

It is important to avoid contamination with other substances which may be more highly allergenic and produce false reactions. A prime example was in the long period of acceptance of chlorogenic acid as the allergen in green coffee (Ref. 51). It was finally revealed that the allergic reaction was the result of a contaminant and that pure chlorogenic acid is not an allergen (Ref. 52).

8. *Stability of food allergens.* Stability differs greatly among food allergens because of variation in different foods in the activity of intrinsic enzymes, intensity of the Maillard reaction, and physiochemical effects in the course of harvesting, processing, storing, and preparation of the food for human consumption, and, finally, the effect of digestive juices before absorption. Of the physical effects in the processing of foods, heat is the most important agent. Heat liability of the allergens in foods varies greatly. Most food retains significant allergenicity at temperatures up-to 100° C. Many, but not all, will lose their allergenicity at temperatures above 120° C (roasting or canning under pressure). A striking example is the loss of allergenic potency of coffee in the roasting process, but not of roasted peanuts which are subjected to equally high temperatures. Although there are reported effects of heat on some food allergens (Refs. 20 and 53) much remains to be documented on the vast number of items in human diets that have as yet not been thoroughly studied. A few foods subjected to heat may increase in allergenicity, possibly by "uncovering" allergenic determinants (Ref. 54).

9. *Skin testing with food extracts.* When properly prepared skin test reagents are used, they appear to be as reliable as pollen extracts in establishing the presence of specific IgE antibodies in the skin. As with pollens, there is an excellent correlation between skin test results and clinical symptoms elicited upon ingestion of the food. From a practical standpoint, food skin tests, although scientifically valid, are often not needed to conform sensitivity in the patient who, through experience, often knows he is clinically sensitive to the food.

Typical allergic reactions due to the ingestion of food, mediated by specific IgE antibodies, are well documented. Food extracts, used in proper dilution, can be helpful and reliable diagnostic agents. A very dilute extract can elicit strongly positive reactions in some patients.

Positive skin reactions, usually of a mild-to-moderate degree that have no clinical relevance, are often elicited with food extracts used in routine diagnostic tests. Some of these reactions may have a specific IgE pathogenesis.

Immediate allergenic reactions with food specific IgE mediation have been documented following the ingestion of the following foods: apple, asparagus, avocado, banana, barley, Brazil nut, cantaloupe, cashew, clams, cocoa, corn, cotton seed, crab, eggs, fish, garbanzo beans (chick pea), grape, green pea, honeydew, lobster, mango, milk, orange, oyster, peach, peanut, pear, pecans, pineapple, pinto beans, potato, rice, scallop, sesame seeds, shrimp, soybean, spinach, tangerine, tomato, vegetable gums, walnut, watermelon, and wheat.

A much larger number of food extracts than those noted above are available for diagnostic testing. It is not known whether all these foods are capble of causing allergic reactions, for example: lettuce and watercress. In all probability, other foods have caused anaphylaxis but have not been documented in the literature, for example, verbal reports of anaphylaxis following ingestion of sunflower seeds, cherry, and raspberry have been made to the Panel. Until more data can be collected, the extracts of well-characterized food substances for which there are no clinical data should remain available for use in skin test diagnosis. Extracts of manufactured foods or undefined source materials which are mixtures or whose composition may vary from time to time should be discontinued.

As with other extracts, reliable measures of potency standardization are needed for food extracts.

10. *Treatment of food sensitivity.* The preferred treatment of IgE mediated food allergy is the avoidance of the offending food. This is easy when foods are served discrete such as seafood or peanuts. Much greater care must be exercised by patients allergic to foods that are mixed with other foods when served and have lost their identifying appearance, odor and taste. "Desensitization" has been attempted (Ref. 55), but was often accompanied by unpleasant gastrointestinal and sometimes serious systemic reactions. Furthermore, any tolerance apparently established by extract therapy tended to be short-lived and difficult to sustain. The precise place of "desensitization" in the treatment of IgE-mediated food allergies is still uncertain; it is not common practice. However, if used, great caution must be exercised in establishing the initial doses of extract.

There are several hundred food extracts available from allergenic extract manufacturers. The list ranges from the common to the exotic. The foods discussed in the generic statements are the only ones that the Panel found to have been studied to any significant degree. In the absence of studies on other specific foods, inferences must be made from the information obtained from these.

Extracts used for provocative testing and neutralizing treatment of non-IgE mediated "allergy" require the same standards of purity, potency, and effectiveness as those used in IgE-medicated allergy. Since the scientific and clinical data required to prove the nature of this type of "allergy" are lacking, the effectiveness of these extracts as therapeutic agents has not been established.

11. *Recommendations.* a. Food extracts should be placed in categories as listed below for use in diagnostic skin testing:

FOOD EXTRACTS RECOMMENDATIONS FOR USE IN SKIN TEST DIAGNOSIS

Extract	Category
Abalone: *Haliotidae* species	IIIA
Alfalfa Leaves: *Medicago sativa*	IIIA
Allspice: *Pimenta officinalis*	IIIA
Almond: *Prunus amygdalus*	I
Anchovy: *Engraulis encrasicholus*	IIIA
Anchovy/Herring/Sardine	IIIB
Angostura Bitters™	IIIB
Anise: *Pimpinella anisum*	IIIA
Anise Seed	IIIA
Apple: *Malus pumila*	I
Apple Mix	IIIB
Apricot: *Prunus armeniaca*	IIIA
Arrowroot: *Maranta arundinacea*	IIIA
Artichoke: *Cynara scolymus*	IIIA
Asparagus: *Asparagus officinalis*	I
Avocado: *Persea americana*	I
Bacon	IIIB
Banana: *Musa paradisiaca sapientum*	I
Barley: *Hordeum vulgare*	I
Barracuda: *Sphraena barracuda*	IIIA
Basil: *Clinopodium vulgare*	IIIA
Bass	IIIA
Bass, Black: *Micropterus* species	IIIA
Bass, Florida Red	IIIA
Bay Leaf: *Laurus nobilis*	IIIA
Bean, Broad: *Vicia faba*	IIIA
Bean, Castor	IIIA
Bean Kidney, Red Kidney: *Phaseolus vulgaris*	IIIA
Bean, Kola	IIIA
Bean, Lima: *Phaseolus*	IIIA
Bean, Mung	IIIA
Bean, Navy	IIIA
Bean, Pinto	I
Bean Sprouts	IIIB
Bean, String/Green	I
Bean, String/Wax	IIIA
Bean, Yellow/Wax	IIIA
Beechnut: *Fagus sylvatica*	IIIB
Beef Meat: *Bos* species	IIIA
Beef heart	IIIA
Beer	IIIB
Beet: *Beta vulgaris*	IIIA
Beet, Sugar, Vegetable	IIIA
Blackberry: *Rubus occidentalis*	IIIA
Black-Eyed Pea: *Vigna sinensis*	IIIA
Blueberry: *Vaccinium corymbosum, pennsylvanicum* or other species.	IIIA
Blue Fish: *Pomatomus saltatrix*	I
Boysenberry: *Rubus ursinatus loganobaccus*	IIIA
Brains, Calves	IIIA
Brazil Nut: *Bertholletia excelsa*	I
Broccoli: *Brassica oleracea italica*	IIIA
Brussel Sprouts: *Brassica oleracea gemmifera*	IIIA
Buckwheat: *Fagopyrum sagittatum*	I
Buttermilk	IIIB
Cabbage: *Brassica oleracea capitata*	IIIA
Cantaloupe: *Cucumis melo cantalupensis*	I
Caraway Seed: *Carum carvi*	IIIA
Cardamon: *Elettaria cardamomum*	IIIA
Carp: *Cyprinus corpio*	I
Carrot: *Daucus carota*	IIIA
Cascara Bark: *Rhamnus purshiana*	IIIB
Casein	I
Cashew Nut: *Anacardium occidentale*	I
Catfish	IIIA
Catfish, Bullhead	IIIA
Catfish, Channel	IIIA
Cauliflower: *Brassica oleracea botrytis*	IIIA
Caviar	IIIB
Celery: *Apium graveolus*	IIIA
Chard: *Beta vulgaris cicla*	IIIA
Cheese, American	IIIB
Cheese, Camembert	IIIB
Cheese, Cheddar (American)	IIIB
Cheese, Cottage	IIIB
Cheese, Limburger	IIIB
Cheese, Mozzarella	IIIB
Cheese, Parmesan	IIIB
Cheese, Pimento	IIIB
Cheese, Provolone	IIIB
Cheese, Romano	IIIB
Cheese, Roquefort	IIIB
Cheese, Swiss	IIIB
Cherry	IIIA
Cherry, Bing: *Prunus avium*	IIIA
Cherry, Choke	IIIA
Cherry, Mix	IIIB
Cherry, Red Sour: *Prunus cerasus*	IIIA
Chestnut: *Castanea dentata*	I
Chewing Gum Base	IIIB

FOOD EXTRACTS RECOMMENDATIONS FOR USE IN SKIN TEST DIAGNOSIS—Continued

Extract	Category
Chicken Meat: *Gallus gallus*	IIIA
Chicle	IIIA
Chicory: *Chichorium intybus*	IIIA
Chili Pepper	IIIA
Chili Powder	IIIB
Chives: *Allium schoenoprasum*	IIIA
Chocolate	IIIB
Cider, Apple	IIIB
Cinnamon: *Cinnamomum zeylanicum*	IIIA
Citron: *Citrus medica*	IIIA
Clams: Hard shell—*Venus mercenaria*	I
Soft shell—*Mya arenaria*	I
Cloves: *Caryophyllus aromaticus*	IIIA
Cocoa	IIIB
Cocoa (Hersheys)	IIIB
Coca-Cola™	IIIB
Cola	IIIB
Cola-Glyoune	IIIB
Cacao, Whole Bean: *Theobroma cacao*	I
Cocoanut: *Cocos nucifera*	IIIA
Codfish: *Gadus callarius*	I
Codliver	IIIA
Collards: *Brassica oleracea acephala*	IIIA
Coffee: *Coffea arabica*	IIIB
Corn: *Zea mays*	I
Corn, Sweet: *Zea mays saccharata*	I
Cotton Seed: *Gossypium* species seed	I
Crab: *Crustacea* species	I
Cranberry: *Vaccinium macrocarpon*	IIIA
Crappie: *Pomoxis* species	IIIA
Crawfish: *Cambarus virilis* and *bartoni*	IIIA
Croaker	IIIA
Cream of Tartar	IIIB
Cucumber: *Cucumis sativus*	IIIA
Cumin Seed: *Cuminum cyminum*	IIIA
Currants: *Ribes* species	IIIA
Currant, Red: *Ribes rubrun*	IIIA
Curry Powder	IIIB
Dandelion Leaf: *Taraxacum officinale*	IIIA
Date: *Phoenix dactylifera*	IIIA
Dill: *Anethum graveolens*	IIIA
Dill Seed or Leaves	IIIA
Dr. Pepper™	IIIB
Duck Meat: *Anas platyrhynchos*	IIIA
Egg, white: (Chicken, *Gallus gallusel*)	I
Egg, whole	I
Egg, yolk	IIIA
Eggplant: *Solanum melongena*	IIIA
Elk Meat: *Cervus canadensis*	IIIA
Endive: *Cichorium endivia*	IIIA
Fig: *Ficus carica*	IIIA
Filbert Nut (Hazelnut): *Corylus species*	IIIA
Fish, White	IIIA
Flounder	I
Frog Meat: *Rana* species	IIIA
Garbenzo (check-pea); *Cicer arietinum*	I
Garlic: *Allium sativa*	IIIA
Gelatin	IIIB
Ginger: *Zingiber officinale*	IIIA
Goat Meat: *Capra* species	IIIA
Goose Meat	IIIA
Gooseberry: *Ribes hirtellum*	IIIA
Grape: *Vitis species*	I
Grape, Concord: *Vitis labrusca*	I
Grape/Raisin Mix	IIIB
Grape, Raisin	IIIB
Grape, Rieber: *Vitis vinifera*	I
Grape, Tokay	I
Grape, White	I
Grape, White Seedless	I
Grapefruit: *Citrus paradisi*	IIIA
Grapefruit Peel	IIIA
Gum, Acacia: *Acacia senegal*	I
Gum, Karaya	I
Gum, Chicle	IIIA
Gum, Tragacanth: *Astragalus* species	I
Haddock: *Melanogrammus aeglefinus*	IIIA
Halibut: *Hippoglossus species*	IIIA
Ham, Smoked	IIIB
Herring: *Clupea* species	IIIA
Hickory Nut: *Carya* species	IIIA
Honey	IIIB
Honey, Pure	IIIB
Hops: *Humulus* species	IIIA
Horseradish: *Armoracia rusticana*	IIIA
Huckleberry: *Gaylussacia baccata*	IIIA
Juniper Berry: *Juniperus communis*	IIIA
Kale: *Brassica oleracea acephala*	IIIA
Kohlrabi: *Brassica oleracea caulorapa*	IIIA
Kola Nut: *Cola acuminata*	IIIA

FOOD EXTRACTS RECOMMENDATIONS FOR USE IN SKIN TEST DIAGNOSIS—Continued

Extract	Category
Lactalbumin	IIIB
Lactalbumin, Alpha, Cow	I
Lactalbumin, Cow's Milk	IIIB
Lactoglobulin, Beta Cow	I
Lamb Meat: *Oris vigrei*	IIIA
Leek: *Allium porrum*	IIIA
Lemon: *Citrus limonia*	IIIA
Lentil: *Lens culinaris*	IIIA
Lettuce: *Lactuca sativa capitata* (iceberg)	IIIA
Lettuce Leaf: *Lactuca sativa Crispa* (leaf)	IIIA
Lettuce Mix: *Lactuca sativa* species	IIIB
Licorice: *Glycyrrhize glabra*	IIIB
Lime: *Citrus aurantifolia*	IIIA
Liver	IIIB
Liver, Beef	IIIA
Liver, Chicken	IIIA
Liver, Pork	IIIA
Lobster: *Homarus americanus*	I
Loganberry: *Rubus ursinus loganobaccus*	IIIA
Mace: *Myristica fragrans*	IIIA
Mackerel: *Scomber scombrus*	I
Malt	IIIA
Mango: *Mangifera indica*	I
Maple, Syrup/sugar: *Acer saccharum*	IIIA
Marjoram: *Majorana hortensis*	IIIA
Melon, Honeydew	I
Milk, Cow's (whole): *Bos* species milk	I
Milk, Condensed	IIIB
Milk (evaporated)	IIIB
Milk, Goat's: *Capra* species milk	IIIA
Millet Grain	IIIA
Mint Mix: Peppermint—*Mentha piperita* and Spearmint—*Mentha spicata*.	IIIB
Mullet: *Mugil cephalus*	IIIA
Mull-Soy™	IIIB
Molasses	IIIB
Mulberry, Red: *Morus rubra*	IIIA
Mulberry, Black: *Morus nigra*	IIIA
Mushroom: *Basidiomycetes* (with species defined).	IIIA
Muskmelon Mix (Cantaloupe/Casaba/Honeydew/Persian): *Cucumis melo*.	IIIB
Mustard, Prepared	IIIB
Mustard Greens: *Brassica juncea*	IIIA
Mustard Seed: *Brassica hirta*	IIIA
Nectarine: *Prunus persica*	IIIA
Nutmeg: *Myristica fragrans*	IIIA
Oat, Whole ground: *Avena sativa*	IIIA
Oatmeal	IIIB
Okra: *Hibiscus esculentus*	IIIA
Olive, Black: *Olea europaea—ripe*	IIIA
Olive, Green: *Olea europaea—green*	IIIA
Olive Mix	IIIB
Onion: *Allium cepa varieties*	IIIA
Onion Mix	IIIB
Orange: *Citrus sinensis*	I
Oregano: *Origanum vulgare*	IIIA
Oyster: *Ostrea virginica*	I
Oyster Plant/Salsify: *Tragopogon porrifolius*	IIIA
Pablum™	IIIB
Papaya: *Carica papaya*	IIIA
Paprika: *Capsicum annuum*	IIIA
Parsley: *Petroselinum crispum*	IIIA
Parsnip: *Pastinaca sativa*	IIIA
Pea, Black Eyed	IIIA
Pea, Green English: *Pisum sativum*	I
Peach: *Prunus persica*	I
Peanut: *Arachis hypogaea*	I
Pear: *Pyrus communis*	I
Pecan: *Carya illinoensis*	I
Pepper, Black: *Piper nigrum*	IIIA
Pepper, Black/White: Piper nigrum	IIIA
Pepper, Cayenne: *Capsicum annuum*	IIIA
Mixed Peppers (Red & Green)	IIIB
Pepper, Green: *Capsicum frutescens*	IIIA
Pepper, Sweet: *Capsicum frutescens*	IIIA
Peppermint: *Mentha piperita*	IIIA
Pepsi-Cola™	IIIB
Perch: *Perca flavescens*	I
Perch, Lake	I
Perch, Sea	I
Persimmon: *Diospyros virginia*	IIIA
Pheasant: *Phasianus torguatas*	IIIA
Pigeon (Squab): *Columbidae* species	IIIA
Pickerel: *Esox* species	IIIA
Pike: *Esox lucius*	IIIA
Pike, Walleye: *Perca*	IIIA
Pimento: *Pimenta officinalis*	IIIA
Pineapple: *Ananas comosus*	I
Pistachio Nut: *Pistacia vera*	IIIA

FOOD EXTRACTS RECOMMENDATIONS FOR USE IN SKIN TEST DIAGNOSIS—Continued

Extract	Category
Plum: *Prunus domestica*	IIIA
Plum, Blue	IIIA
Plum/Prune Mix	IIIB
Plum, Red	IIIA
Poke Greens: *Phytolacca americana*	IIIA
Pollock	IIIA
Pomegranate: *Punica granatum*	IIIA
Pompano: *Trachinotus carolinus*	IIIA
Popcorn Seed: *Zea Mays*	IIIB
Poppy Seed: *Papaver somniferum*	IIIA
Pork	IIIA
Postum™	IIIB
Potato, Red Irish: *Solanum tuberosum*	I
Potato, Sweet: *Ipomoea batatas*	IIIA
Potato, White Irish: *Solanum tubersum*	I
Prune, Fresh	IIIA
Prune, Dried	IIIB
Psyllium Seed: *Plantago pysllium*	IIIA
Pumpkin: *Cucurbita pepo*	IIIA
Quail: *Colinus virginianus*	IIIA
Quince: *Cydonia oblonga*	IIIA
Quince Seed	IIIA
Rabbit: *Leput* species	IIIA
Radish: *Raphanus sativus*	IIIA
Raisin	IIIB
Raspberry: *Rubus* species	IIIA
Raspberry, Black: *Rubus occidentalis*	IIIA
Raspberry, Red: *Rubus idaeus*	IIIA
Red Snapper: *Lutjanus campechanus*	IIIA
Rhubarb: *Rheum rhaponticum*	IIIA
Rice: *Oryza sativa*	I
Rice, Wild	IIIA
Root Beer	IIIB
Rosemary: *Rosmarinus officinalis*	IIIA
Rutabage: *Brassica napobrassica*	IIIA
Rye: *Secale cereale*	IIIA
Saccharose	IIIB
Saccharin	IIIB
Safflower Seed: *Carthamus tinctorius*	IIIA
Sage: *Salvia officinalis*	IIIA
Salmon: *Oncorhynchus* species	I
Sardine: *Sardina pilchardus*	IIIA
Savory: *Satureia hortensis*	IIIA
Scallops: *Pecten irradians*	I
Sesame Seed: *Sesamum indicum*	I
Seven-up™	IIIB
Shad: *Alosa sapidissima*	IIIB
Shrimp: *Peneus setiferus*	I
Smelt: *Osmerus mordax*	IIIA
Snail: *Helicidae* species	IIIA
Sole: *Achirus fasciatus*	I
Sorghum: *Sorghum vulgare* species	IIIA
Soybean: *Glycine max*	I
Spearmint: *Mentha spicata*	IIIA
Spinach: *Spinacea oleracea*	I
Squash: *Cucurbita pepo* varieties	IIIB
Squash, Acorn: *Curcubita pepo* varieties	IIIA
Squash Mix	IIIB
Squash, Banana	IIIA
Squash, Summer	IIIA
Squash, Tomato	IIIA
Squash, Turnip	IIIA
Squash, Water Cress	IIIA
Squash, Zucchini (Italian)	IIIA
Squirrel: *Sciurus* species	IIIA
Strawberry: *Fragaria* species	IIIA
Sugar (Beet): *Beta vulagaris*	IIIB
Sugar (Cane): *Saccharum officinarum*	IIIB
Sugar (Maple): *Acer saccharum*	IIIB
Sunfish (Bluegill): *Lepomis* species	IIIA
Sunflower Seed: *Helianthus* species	IIIA
Sweetbreads	IIIB
Swiss Chard: *Beta vulgaris cicla*	IIIA
Swordfish: *Xiphias gladius*	IIIA
Syrup: Pure Maple	IIIB
Tangerine: *Citrus nobilis*	I
Tapioca: *Manihot esculenta*	IIIA
Tea: *Thea sinensis* (if variety is defined)	IIIA
Tea: Black	IIIB
Tea: Green	IIIB
Tea: Mixed	IIIB
Thyme: *Thymus vulgaris*	IIIA
Tomato: *Lycopersicon esculentum*	I
Trout: *Salvenlinus* (if species is defined)	IIIA
Trout: Gulf or Speckled	IIIA
Trout, Lake: *Salvelinus namaycush*	IIIA
Trout, Rainbow: *Salmo irideus*	IIIA
Tuna: *Thunnus* species	IIIA
Tuna: Mix	IIIB
Turkey (meat): *Agriocharis ocellata*	IIIA

FOOD EXTRACTS RECOMMENDATIONS FOR USE IN SKIN TEST DIAGNOSIS—Continued

Extract	Category
Turmeric: *Curcuma longa*	IIIA
Turnip: *Brassica rapa*	IIIA
Turnip Greens	IIIA
Vanilla Bean: *Vanilla planifolia*	IIIA
Venison (Deer): *Odocoileus* species	IIIA
Vinegar	IIIB
Walnut, Black: *Juglans nigra*	I
Walnut, English: *Juglans regia*	I
Watercress: *Lepidium sativum*	IIIA
Watermelon: *Citrullus vulgaris*	I
Wheat, Whole: *Triticum* species	I
Whitefish: *Coregonus clupeiformis*	IIIA
Whiting: *Merlangus merlangus*	IIIA
Worcestershire Sauce	IIIB
Yam: *Dioscorea alata*	IIIA
Yeast: *Saccharomycetaceae*	IIIB
Yeast, Bakers' (if species is defined)	IIIA
Yeast, Distillers' (if species is defined)	IIIA
Yeast Mix (Bakers/Brewers)	IIIB

b. The above food extracts which are recommended to remain on the market for skin test diagnosis should be placed in Category IIIA for immunotherapy to allow a reasonable period of time for appropriate studies to establish their safety and effectiveness for this use. Those food extracts recommended for Category IIIB for skin test diagnosis should also be placed in Category IIIB for immunotherapy. Labeling of food extracts used for treatment to reduce IgE-mediated sensitivity should include a special warning statement to alert the physician of the hazard associated with the use of the extract in treatment.

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IV. Allergenic Extracts—Product Recommendations

The Panel reviewed the data submissions of all manufacturers licensed to produce allergenic extracts (BER Volume 4001 through 4042). Although these data submissions supplied general information supporting the value of various allergenic extracts, the data were insufficient to place any company's product in Category I, primarily because of a lack of correlation of the potency and specificity of the extracts in current production with those used in the reported controlled clinical trials. Although the Panel recommended that several products be placed in Category I on a generic basis relying on the accumulated evidence about the product, the generic Category I recommendation for an extract should not be applied to any company's spescific product.

Therefore, each reviewed allergenic extract product of the licensed manufacturer is recommended to be placed in category IIIA if the Panel recommended that the respective extract be placed in Category I on a generic basis. For extracts which the Panel made a generic recommendation of Category II, Category IIIA, or Category IIIB, the Panel recommends that each manufacturer's product be placed in the same category as the respective generic extract.

The result of these recommendations is that no allergenic extract products as described by the manufacturers in their 1974 data submissions to the Panel were recommended to be placed in Category I. The Panel's recommendations place most allergenic extract products in Category IIIA with the belief, as stated earlier, that if appropriate studies are conducted, many of them will be found to be effective.

Several newer allergenic products such as the hymenoptera venoms or short ragweed pollen extracts which have potency standards were recently licensed by FDA because there are clinical data demonstrating safety and effectiveness and because their potency can be related to the materials for which the clinical data were developed. When this type of data, as described earlier in the section on "Recommendations for Further Testing of Category III Allergenic Extracts," is developed for a Category III product, the product should then be approved by the FDA for Category I.

V. Alum-Precipitated Allergenic Extracts

1. *Generic statement*—a. *Introduction.* Immunological adjuvants are used extensively to enhance the immune response to viral and bacterial vaccines (Ref. 1). The manner in which some adjuvants improve the efficiency of the immunizing process is to slow the

absorption of antigen from the injection site, thereby prolonging the contact of the antigen with macrop–hages and lymphocytes. This repository action of adjavant permits the use of a smaller dose of antigen and fewer injections to obtain the same level of immunization achievable without it.

Immunotherapy for allergic diseases, even more so than for infectious diseases, has been limited by the amount of allergen that can be administered in a single dose, a limitation that has been responsible for the very large number of injections usually administered. The bulk of a dose of water soluble allergenic extract which is injected subcutaneously promptly enters the circulation and is metabolized. Few molecules remain to enter the lymphatics and act on the immunological system.

It is not surprising then to find that, early on, allergists experimented with methods that would prolong retention of allergens at sites of injection and thereby permit a reduction in the frequency of injections during therapy. Cold compresses on the injection site and the inclusion of epinephrine with allergenic extracts, both aimed at inducing local vasoconstriction, were among the first methods used. These methods made it possible to give higher doses without systemic reactions, but were later abandoned because they were relatively ineffective.

b. *Repository adjuvants.* The most commonly used repository adjuvants have been aluminum compounds and water-in-oil emulsions. The most widely use of these in allergy have been aluminum compounds, which are also the only repository preparations currently licensed for use in therapy. Although water-in-oil emulsions have been used experimentally by some physicians, they are not licensed products and therefore were not reviewed by this Panel.

Many antigens are easily absorbed onto colloidal aluminum salts, and such alum precipitates will retain the antigen in high local concentration at the site of injection and then release it slowly thus permitting greater access to the lymphatic system. Antibody-producing plasmacytes develop in the lymph nodes draining an injection site in greater numbers and over a much longer period of time when the antigen is injected in the alum-precipitated state than when the same dose of antigen is injected in aqueous solution (Ref. 2). There is no evidence that adsorption on aluminum salts alters the antigenic specificity of proteins. However, injection of antigen absorbed on alum enhances the production of IgE antibodies in laboratory animals and man.

c. *Effectiveness of alum-precipitated allergenic extracts.* Alum-precipitated allergenic extracts are not licensed for use in diagnosis. Alum-precipitated allergenic extracts have been used in therapy for at least 35 years. During this period controlled clinical trials have demonstrated that certain alum-precipitated shore ragweed pollen extracts are equally as effective as the aqueous extracts in controlling the symptoms of ragweed hay fever. (See below for refs.) Likewise, the immune response as measured by serum IgG antibody levels was similar with both types of extract (Ref. 3). To the extent that fewer injections are required, alum-precipitated extracts might be regarded as advantageous (Ref. 4). Because allergens which are extracted in an alkaline-pyridine medium before adsorption onto alum respresent a different type of product, they are considered separately below.

d. *Safety of alum-precipitated allergenic extracts.* The subcutaneous injection of alum-precipitated vaccines and allergenic extracts can produce small granulomatous nodules at the site of injection; this is not found with aqueous extracts. However, wide use of alum-precipitated extracts has not been associated with a significant incidence of such nodules. The amount of aluminum administered with these preparations (not more than 0.85 mg per mL) is far below the acute toxic threshold for this metal in man (Ref. 5). The Panel found no other significant short-term toxicity or adverse reactions which could be attributed to the use of aluminum-containing adjuvants.

The number of systemic allergic reactions associated with alum-precipitated allergenic extracts is reported to be lower than with aqueous preparations (Ref. 4).

In in vitro screening of metal salts for mutagenicity, aluminum sulfate was found not to decrease the fidelity of DNA synthesis, and therefore it behaved negatively in a test in which a large number of metals known to have carcinogenic propensity were found to be positive (Ref. 6).

The oncogenic potential of aluminum compounds administered to human subjects and to test animals, however, has been a matter of concern to the Panel and to the FDA. Alum-precipitated allergenic extracts have been used widely in the past 15 to 20 years, and alum-precipitated diphtheria toxoid has been used for immunization for over 35 years. During this era millions of individuals have received injections containing alum; some allergic patients have been repeatedly administered injections containing alum for as long as a decade. Nevertheless, the Panel found no report which suggests that neoplasms occur more frequently in treated patients than in the general population.

Jekel et al. searched the Connecticut Tumor Registry and found no increase in the occurrence of upper arm soft tissue sarcomas before and after the introduction of alum-precipitated allergenic extracts (Refs. 7 and 104). Sarcoma was selected for study because of its occurrence in some strains of mice at injection sites of aluminum salts and other adjuvants (Ref. 8). It is this latter evidence which was the focus of concern about the risk of administering alum-precipitated allergenic extracts to man. The study was conducted by the Midwest Research Institute (MRI) for the Bureau of Biologics, Food and Drug Administration, between 1967 and 1974. The test consisted of two parts, determination of complete (direct) carcinogenic activity and determination of cocarcinogenic activity, following subcutaneous injection of various materials into three strains of mice. Details of the protocols are given in the final report from MRI (Ref. 8).

The results can be summarized as follows: (1) There was a pronounced difference in the frequency of tumors among three strains of mice and some difference between the sexes; (2) virtually all adjuvants tested were cocarcinogenic to subcutaneously injected bidenz[a,h]anthracene (DAB), and the aluminum-containing materials were in general more active than the others in this respect; (3) although the tests for complete carcinogenic activity were much more variable, they seem to indicated that aluminum-containing materials are carcinogenic at least in some strains of mice.

Interpretations of this study by leading experimental oncologists have varied greatly (Refs. 9 through 11). All agree that the relevance of these animal data to man is not known at the present time, especially in light of the negative data associated with more than 15 years of marketing experience with alum-precipitated allergenic extracts in the treatment of humans and the even longer experience with alum-precipitated bacterial vaccines. The animal experiments were associated with significant problems in husbandry which some experts interpreted to have seriously influenced the results (Ref. 11). Wide variation in the response of the control groups introduced questions about the purity of the mouse strains. The cocarcinogen experiments with

DBA were questioned as being irrelevant for man. Finally, the MRI study was viewed by the Panel as suggesting, but not proving, that aluminum may have carcinogenic potential, and that its use in man is accompanied by a risk which is probably quite low. The Panel suggested that the MRI study should be modified in design and repeated under more favorable conditions should FDA decide that the risk is sufficiently great that it would consider placing a ban on the use of aluminum-containing biological products now being administered to humans. Additionally, the testing of these substances in nonrodent animals was suggested as a more relevant model of the human experience.

Elevated aluminum levels found in cerebral cortex tissue of patients with Alzheimer's disease, dialysis dementia or similar encephalopathies have suggested that aluminum ions may cause long-term cumulative toxic effects (Refs. 82 through 86). Since each dose of an alum-precipitated allergenic extract may contain up to 0.85 milligram of aluminum (Ref. 87), weekly administration of these extracts at the maximal recommended dose will add several milligrams of aluminum to the usual intake. Although chronic toxicity of injected aluminum has not been systematically evaluated, this amount of aluminum probably does not present a toxic hazard to an individual with normal renal function. While the daily dietary intake of aluminum ranges from 10 to 100 milligrams, only a small portion of this intake is absorbed (Ref. 88). The serum aluminum level in healthy persons is about 1.4 milligrams per liter, as determined by neutron activation (Ref. 89), or 0.17 to 0.43 milligram per liter when assayed by other methods (Refs. 89 through 91). Normal excretion in urine is about 1 microgram per kilogram of body weight per day (Ref. 92).

The relationship of aluminum and its possible role in dementia has been studied and reviewed by Arieff et al. (Ref. 88). They concluded that an elevated brain aluminum ion content probably does not cause dialysis dementia or the EEG findings typical of disalysis dementia. They estimated that less than 7 milligrams of aluminum was present in the total brain of patients with dialysis demantia. Th serum level of aluminum may be as high as 110 milligrams per liter in patients given oral aluminum resins, and urinary excretion may approach 250 milligrams per day in hyperaluminemic patients (Ref. 89). There appear to be many other factors. such as genetics (Ref. 93), phosphate depletion (Ref. 94), altered gastrointestinal absorption (Ref. 95), high dialysate aluminum concentration (Ref. 96), and blood-brain barrier disorders (Ref. 88), which may be associated with dementia and aluminum retention in the brain. Studies being conducted at Duke University Medical Center, supported in part by the National Institute of Aging, Research Grant AGO–1086, to investigate various clinical, laboratory and epidemiologic factors (including aluminum tissue levels and allergenic extract medication history) that may be associated with the development of senile dementia of the Alzheimer's type, may help clarify this issue.

e. *Summary, alum-precipitated allergenic extracts.* Alum containing allergenic extracts are the most widely used adjuvant preparations in allergy practice today. The addition of a precipitant to allergenic extracts appears to have been a useful means to facilitate the administration of larger doses at less frequent intevals to sensitive human subjects.

Experience has shown that some alum-precipitated extracts are equally as effective as aqueous extracts and can be administered less frequently. Immunological monitors such as histamine release studies and IgG antibody levels are similar with the two types of preparations.

No adverse reactions of any consequence have been reported to be associated with the administration of alum-precipitated allergenic extracts to humans. Toxicologic studies have indicated that mice have a tendency toward sarcoma formation at the site of injection of alum. However, technical problems have placed the validity of the studies in question. Epidemiological studies of soft tissue sarcomas in man fail to establish a relationship to prior aluminum adjuvant injections.

Although higher brain levels of aluminum in patients have been associated with dementia, evidence of its causal relationship is still circumstantial, and the Panel did not find sufficiently compelling evidence to recommend a change in the permitted levels of aluminum in allergenic extracts.

f. *General recommendations for alum-precipitated allergenic extracts.* The Panel has reviewed evidence dealing with the use of aluminum-containing adjuvants in immunotherapy for allergic disease. In some examples studied, immunological and clinical evidence suggests results comparable to those following the use of aqueous extracts. The margin of difference is not great and falls far short of the enhancing effect which might be expected from the larger doses of extract administered with alum. Nevertheless, the principle embraced by adjuvant therapy is sound, and its further development should be encouraged.

2. *Product review, alum-precipitated allergenic extracts (Center-Al™), Center Laboratories, Inc., Port Washington, New York.* Alum-precipitated allergenic extracts are prepared from aqueous extracts by formation of an aluminum hydroxide precipitated complex and are licensed for use in immunotherapy only. A large number of mixtures and individual extracts are marketed under the product license. Examples as listed in the data submission from Center Laboratories (Ref. 17) include:

Mixtures

Mixed Ragweed (Tall and Short Ragweed)
Mixed Weeds (Cocklebur, Pigweed, English Plantain, Lamb's Quarters)
3 Mixed Grasses (Bermuda, Johnson, Brome)
5 Mixed Grasses (Timothy, Orchard, June, Red Top, Sweet Vernal)
6 Mixed Grasses (Timothy, Orchard, June, Red Top, Meadow Fescue, Perennial Rye)
Southern Grass Mixture (One-third each: Johnson, Bermuda, and the above "6 Mixed Grasses" Mixture)
Mixed Trees (Ash, Beech, Birch, Elm, Hickory, Maple, Oak, Poplar)

Individual Extracts

Bermuda Grass
Perennial Rye Grass
Marsh Elder
Russian Thistle
Western Ragweed
Dust
Weed Pollens
Grass Pollens
Tree Pollens
Sycamore
English Plantain
House Dust
Pecan Pollen
Walnut Pollen
Molds
Inhalants
Epidermals

a. *Alum-precipitated aqueous ragweed pollen extracts.* As with aqueous extracts, the alum-precipitated ragweed pollen extract has been studied most extensively. Alum-precipitated ragweed pollen extract is effective in the treatment of ragweed hay fever, based on the following evidence:

(1) An increase in ragweed specific IgG "blocking" antibody has been demonstrated in ragweed-sensitive

patients during therapy (Refs. 3, 4 and 12 through 14).

(2) An increase in ragweed specific IgE antibody occurs in ragweed-sensitive patients shortly after the start of immunotherapy, then there is a progressive fall in the level of this antibody during the course of immunotherapy; and blunting of the expected increase in antibody level is seen following natural exposure to pollen during the ragweed season (Refs. 4 and 12).

(3) A decrease in patient's basophil sensitivity to ragweed allergen after therapy has been reported (Ref. 3).

(4) The reduction in the severity of symptoms of ragweed hay fever was greater in patients who received alum-precipitated ragweed pollen extract than in patients who were given placebo but not greater than in patients treated with a comparable dose of aqueous ragweed extract (Refs. 3, 4 and 12).

There are uncontrolled studies which report clinical benefit following the administration of alum-precipitated aqueous, ragweed pollen extracts (Refs. 13 and 14).

b. *Other alum-precipitated aqueous extracts.* There are only meager reports concerning other types of alum-precipitated aqueous exptracts.

Norman et al. showed that 8 of 11 grass-sensitive patients developed detectable rises in specific IgG-blocking antibodies following the administration of alum-precipitated grass extract as measured by blocking of leukocyte histamine release with serum (Ref. 3). The clinical effectiveness of this treatment was not determined in this study.

Marsh and coworkers showed that both specific IgG and IgE antibody responses occurred in a small number of normal individuals following the administration of alum-precipitated grass extract (Ref. 15). The same group reported that several of these previously nonallergic individuals experienced symptoms of hay fever during a subsequent grass pollen season (Ref. 103). These observations raise the theoretical possibility that as a result of therapy with an alum-precipitated extract, some allergic patents may develop heightened sensitivity to one or more allergens to which they were previously not allergic.

Data collected by Center Laboratories on 80 patients receiving aqueous house dust extract or Center-Al house dust extract showed no difference between the two groups in the number of local and systemic reactions and in the number of injections required to reach the proposed maximum dose per injection (Ref. 17). No measure of clinjcal effectiveness or immunological response was determined in this study.

None of the above reports establishes a clear-cut advantage for alum-precipitated over aqueous extracts. Less frequent injections are possible with alum-precipitated extracts, and perhaps fewer or milder reactions occur with their use, but the differences are not remarkable. At the same time, there is no substantial evidence of an added risk associated with their administration.

c. *Conclusions and recommendations*—(1) On the basis of evidence of a generic nature, adsorption of aqueous allergenic extracts onto colloidal salts of aluminum does not appear to alter the antigenicity of the active components of allergenic extracts.

(2) On the basis of limited clinical and laboratory evidence, at least aqueous extracted alum-precipitated short ragweed pollen extract appears to be as effective as aqueous mixed ragweed pollen extract in the treatment of ragweed hay fever, although it is not know whether the adsorption onto aluminum changes the actual dose of allergen needed to achieve adequate clinical and immunological responses. The margin of difference between the alum-precipitated and the aqueous extracts is not great and seems to fall short of the enhancing effect which might be expected from the apparently larger doses of extract administered with alum. Nevertheless, the possibility of giving injections less frequently and perhaps of inducing fewer systemic allergic reactions does give alum-precipitated ragweed pollen extract an advantage over the aqueous extract.

(3) There is insufficient evidence in the case of alum-precipitated extracts other than ragweed pollen to allow the Panel to judge their effectiveness in the treatment of allergic diseases. Still it is likely that results with these extracts will parallel ragweed pollen extract with respect to their corresponding aqueous extracts.

(4) Adequate evidence should be obtained that adsorption of allergenic extracts onto alum does not alter the immunologic properties of the extracts.

(5) A method to measure the amount of allergenic extract adsorbed onto alum must be developed so that the potency of these products can be determined accurately.

(6) Regarding the safety of these products, experimentation with aluminum-containing adjuvants has suggested a potential, but not clearly defined oncogenic hazard, associated with their injection into mice. Since the experiments were done imperfectly, the Panel recommends they be repeated with better controls and under more favorable conditions of husbandry and that a nonrodent animal model more relevant to man be added to the experimental protocol. Based on limited evidence, it appears that the widespread use of alum-precipitated vaccines and allergenic extracts in medical practice over a number of years has not been associated with sarcomas or any other neoplasm in man. In the opnion of the Panel, this clinical experience weighs heavily in favor of permitting the continued use of these preparations. However, recognizing that repeated administrations of a carcinogen over many years, or a long latent period after exposure, may be necessary before a cancer becomes clinically evident, the Panel recommends continued surveillance of patients receiving aluminum extracts for the development of lesions, particularly at sites of injection.

(7) The Panel recommends that each alum-precipitated allergenic product for which Center Laboratories, Inc., is licensed be placed in the same generic category as the corresponding aqueous product.

3. *Product review, alkaline-pyridine extracted alum-precipitated allergenic extracts (Allpyral™), Dome Laboratories, Division of Miles Laboratory, West Haven, Connecticut.* Allpyral™ products are prepared from nondefatted source materials by a procedure similar to that originally outlined by Fuchs and Strauss (Ref. 18). The essential features of this method included: (1) Extraction in a very alkaline medium containing pyridine, (2) 24-hour extraction time at room temperature, (3) the addition of potassium alum in sulfuric acid to the alkaline pyridine extract, (4) separation of the resulting alum precipitate by centrifugation, and (5) washing the precipitate using sterile saline solution. Originally, alkalinity was achieved with 0.3 M sodium bicarbonate. Since 1963, 0.1 N sodium hydroxide has been used, giving a pH of about 12. Furthermore, extraction times up to 6 days are currently used by this manufacturer.

A large variety of extracts of single substances and of mixed extracts are manufactured and licensed for use in therapy and are sold under the trademark name of Allpyral™.

Allpyral™ extracts listed by the manufacturer include:

Tree Pollen Extracts

Acacia Mix (acacia spp.)
Alder, Red
Alder, Tag

Ash Mix (American & Pennsylvania Ash)
Ash, Arizona
Ash, Oregon
Beach
Birch Mix (*Betula lenta* & *B. Nigra*)
Box Elder
Cedar, Mountain
Cottonwood, Fremont
Cottonwood, Western
Elm Mix (American & Chinese Elm)
Elm, Chinese
Hazelnut, California
Hickory
Maple Mix (*Acer saccharum, A. rubrum, A. saccharinum,* & *A. macrophyllum*)
Mesquite
Mulberry Mix (*Morus alba* & *M. rubra*)
Oak Mix (*Quercus rubra, Q. alba, Q. agrifolia,* & *Q. virginiana*)
Oak, California Live
Olive
Pecan
Poplar Mix (*Populus alba, P. deltoides*)
Sweet Gum
Sycamore, Eastern
Walnut Mix (*Juglans nigra, J. californica, J. regia*)
Willow Mix (*Salix nigra S. alba*)
7 Tree Mix (Ash mix, Beech, Birch mix, Elm mix, Hickory, Oak mix & Poplar mix)
10 Tree Mix (Tag Alder, Ash mix, Elm mix, Beech, Birch mix, Maple mix, Hickory Oak mix, Poplar mix, E. sycamore)

Grass Pollen Extracts

Bermuda
Blue, Annual
Blue, Canada
Blue, Kentucky
Brome
Canary, Reed
Corn Pollen
Johnson
Meadow Fescue
Orchard
Quack
Red Top
Rye, Alkali
Rye, Giant Wild
Rye, Italian
Rye, Perennial
Salt
Sweet Vernal
Timothy
Velvet
Wheatgrass, Western
2 Grass Mix (Timothy & Orchard)
3 So. Grass Mix (Bermuda, Johnson & Brome)
7 Grass Mix (Orchard, Timothy, Kentucky Blue, Sweet Vernal, Perennial Rye, Meadow Fescue & Red Top)
9 So. Grass Mix (Johnson, Bermuda & 7 Grass Mix above)

Weed Pollen Extracts

Careless Weed
Cocklebur
Greasewood
Kochia
Lamb's Quarters
Marsh Elder Mix
Mugwort, Common
Pigweed, Rough
Pigweed Spiny
Plantain, English
Ragweed, False
Ragwee, Mixed (Short & Tall)
Ragweed, Short
Ragweed, Tall
Ragweed, Western
Russian Thistle
Sagebrush, Common
Scale, Mixed (*Atriplex canescens, A. polycarpa, A. wrightii*)
Sheep Sorrel
Sugar Beet
Western Water Hemp
Wormwood Annual
Yellow Dock
National Weed Mix (Ragweed mix, Cocklebur, Lamb's Quarters & Rough Pigweed)
Western Weed Mix (Russian Thistle, Kochia, Western & False Ragweed & Common Sagebrush)

Epidermal Extracts

Cat
Cattle
Dog
Feather Mix (Chicken, Duck & Goose)
Horse
Rabbit
Sheep Wool

Inhalant Extracts

House Dust
Grain Mill Dust

Mold Extracts

Alternaria tenuis
Aspergillus fumigatus
Botrytis cinerea
Candida albicans
Cladosporium herbarum
Curvularia lunata
Epicoccum purpurascens
Fusarium oxysporum
Helminthosporium sativum
Hormodendrum hordei
Mucor racemosus
Penicillium notatum
Phoma betae
Pullularia pullulans
Rhizopus arrhizus
Stemphylium botryosum
Trichophyton mentagrophytes
Trichothecium roseum
4 Mold Mix (*Alternaria, Aspergillus, Hormodendrum, Penicillium*)

Stinging Insect Extracts

Honeybee
Hornet
Wasp
Yellow Jacket
Stinging Insect Mixture (Honeybee, Hornet, Wasp & Yellow Jacket)

a. *Allpyral™* ragweed extracts. As with other allergenic products, the ragweed pollen extracts have been studied most extensively. These studies have raised serious questions regarding the potency and effectiveness of Allpyral™ ragweed extracts for their labeled use in immunotherapy.

(1) Goodman and Harris (Ref. 19) studied the pyridine extraction, alum-precipitation method of preparation of ragweed pollen extract from a chemical viewpoint. They found that only 25 percent of the alkaline pyridine-extracted ragweed pollen allergen was absorbed to the alum while 75 percent remained unabsorbed and was discarded in the process. They concluded that "The highly alkaline pryidine-bicarbonate extracting fluid and long contact time of extraction denature antigenic sites."

(2) Winkenwerder and Norman (Ref. 60) compared Allpyral™ rageweed pollen extract and antigen E. Sixty previously untreated patients were divided into three groups and given either Allpyral™ ragweed pollen extracts, antigen E or placebo injections. Somewhat low doses of the Allpyral™ extract (up to 1,000 to 2,500 PNU) and the antigen E (0.5 to 2.0 mcg) were given. Careful symptom diaries were kept. This study included a double-blind evaluation of results. Upon analysis of these diaries, there was no difference in the clinical result between the three groups. In 1964, the same groups, plus a group which received aqueous whole ragweed pollen extracts were compared. The final Allpyral™ extract doses were as high as 1,500 to 10,000 PNU. The final aqueous doses were still rather low however, (10 to 1,000 PNU). The placebo group had slightly more symptoms than the other groups, but the differences were not statistically significant. It was concluded that this study failed to show effectiveness of any of the materials used for treatment.

Critique: The study was carried out in a well-controlled manner. The doses of aqueous ragweed extract and antigen E were low compared to doses found to be effective in more recent studies.

(3) Lichtenstein (Refs. 20 and 21) reported that ragweed antigen E appeared to be destroyed in the preparation of Allpyral™ ragweed pollen extract. The antigenicity of Allpyral™ and aqueous ragweed pollen extracts was studied by measuring the IgG antibody response to antigen E in

patients following treatment (Ref. 54). All patients treated with aqueous extract had increased IgG antibody levels, whereas patients treated with Allpyral™ over 3 to 4 years essentially had no evidence of a IgG antibody response to antigen E. This study showed that at least the antigenicity of antigen E is eliminated by this process of extracting and precipitation.

(4) Reisman and Arbesman (Ref. 22) reported the Allpyral™ ragweed pollen extract was relatively ineffective in the treatment of ragweed hay fever. Forty-six patients were treated preseasonally for about 2 months with Allpyral™ ragweed up to a maximum dose of 20,000 PNU. Clinical results were assessed on the basis of patient symptom scores and weekly examinations. In addition, hemagglutinating antibody titers against whole ragweed extract were measured. Eighteen of the 46 Allpyral™ treated patients were considered as having satisfactory clinical results. There was no relationship between the clinical result and the total dose of extract administered. Eight patients who had systemic reactions to very low doses of aqueous extract were able to tolerate much higher doses of Allpyral™ ragweed with no trouble, suggesting that the Allpyral™ extract contained much less of the relevant allergens. Six patients on Allpyral™ ragweed were later given much lower doses of aqueous extract and three of them had severe systemic reactions. Hemagglutinating antibody titers following treatment with Allpyral™ ragweed rose in only two patients, decreased in three and remained the same in seven. In contrast, approximately 80 percent of the 40 patients treated with an aqueous preparation containing the delta fraction of ragweed pollen extract had a satisfactory response and had significant rises in hemagglutination titers as well. These authors concluded that Allpyral™ ragweed pollen extract was poor antigen and lacked significant allergenic activity.

(5) Speigelman, Friedman, and Tuft reported hemagglutinating antibody titer changes after the use of Allpyral™ ragweed pollen extracts. In an article reporting their experience with 92 patients, 62 percent of the patients showed no antibody change after treatment, 28 percent had a 2 to 4 fold increase, 4 percent had an 8 or more fold increase and 6 percent had a drop (Ref. 23). In a later report, they found that 4 patients had no change in antibody titer, 6 patients had a 2 fold increase, 10 patients a 4 fold increase and 3 patients an 8 fold increase (Ref. 24). Whether these changes were significant could not be determined.

(6) Additional data concerning Allpyral™ ragweed pollen extract were presented to the Panel by representatives of Dome Division of Miles Laboratories, Inc. (Ref. 81):

(i) The manufacturing process used to produce Allpyral™ ragweed pollen extract in the United States was reviewed. The Panel was informed that Dome Laboratories have extracted nondefatted ragweed pollen with pyridine and 0.1 N sodium hydroxide since 1963 (Ref. 16). At the 25th meeting of the Panel, it had been erroneously inferred that the extraction was done with pyridine and 0.3 M sodium bicarbonate. The Panel took note of this error.

(ii) Until 1972, the extraction time was variable and sometimes was as long as 89 days. Since 1972, the maximum extraction was limited to 6 days.

(iii) Data were presented showing the effect of the two extracting fluids, pyridine-bicarbonate and pyridine-sodium hydroxide, on the PNU content of the product. Extraction was carried out for varying time periods. PNU recovery increased as the extraction time increased from 1 day to 22 days. The yield, based on PNU content, was somewhat greater with the pyridine-sodium hydroxide extracting fluid than with pyridine sodium bicarbonate extracting fluid.

(iv) Hemagglutinating antibodies against aqueous ragweed-pollen-sensitized sheep red blood cells were induced in CFW mice using three different Allpyral™ ragweed pollen preparations prepared with extracting times of 5, 16, and 89 days, respectively. The highest antibody titers were found in those mice receiving the material extracted for 5 days. Titers were lower in mice that received material extracted for 16 days and were almost nonexistent in mice that received material extracted for 89 days. Only two mice were used in each of the experiments, thus limiting the accuracy of the data. Control experiments were not carried out with aqueous ragweed pollen extract or a simple alum-precipitated aqueous ragweed pollen extract. These data may have been partly responsible for the reduction of the maximum extraction period to 6 days as noted above. Clinical and immunologic studies carried out prior to 1972 were, therefore, possibly not relevant for the currently marketed product.

(v) In an attempt to show that Allpyral™ ragweed pollen extract contains antigen E, guinea pigs were immunized with a single intraperitoneal injection of 50,000 PNU Allpyral™ ragweed pollen extract. The active cutaneous anaphylaxis model was used to detect the presence of antobodies to antigen E. After a 2-week period, the animals were challenged intradermally with antigen E. The two guinea pigs immunized with Allpyral™ ragweed pollen extract had fairly immediate strong skin reactions to challenge with 2 micrograms of antigen E. Two guinea pigs immunized with alum-precipitated aqueous ragweed had similar strong reactions to antigen E. Only one control guinea pig was used in these experiments, and it had an equivocally positive reaction to a similar challenge dose of antigen E. When the animals were challenged with 0.2 microgram of antigen E, skin reactions were much less intense, and there was very little difference between the control and immunized animals.

The Panel noted that, again, very few animals were used in this experiment. The response in the one control animal which was challenged with the highest dose of antigen E suggested that this dose might have induced a nonspecific, i.e., irritative, rather than an immunologically specific reaction. No attempt was made to test the animals' sera for antibody by the passive cutaneous anaphylaxis method as is ofter done when looking for an anaphylactic antibody response.

(vi) In response to questioning, the Dome representative stated that the pH during the extraction process was approximately 12. This pH usually denatures most proteins. In studies reported previously by King et al. (Ref. 97), pH of 10 or above was shown to significantly denature antigen E.

(vii) In response to questioning, the Dome representative stated that antigen E could not be detected by radial immunodiffusion in the pyridine extracted ragweed solution prior to the addition of alum. This method is used for the measurement of antigen E in commercial extracts: its lower limit of detection is 5 micrograms per milliliter. FDA has proposed that the lower limit of antigen E content in a 1:10 extract of short ragweed pollen extract be 135 micrograms per milliliter (Ref. 98).

Critique: The major criticisms of Allpyral™ ragweed pollen extract have been the lack of detectable antigen E in this preparation and its lack of immunogenicity in experimental animals and humans. It is possible that the results of the active cutaneous anaphylaxis experiments were valid; however, the protocol by Dome was too inadequate to allow the Panel to judge their merit. It is also possible that mice

would respond to immunization with Allpyral™ ragweed pollen extract because there may well be protein (albeit denatured) in this material to which the animals would respond. The relevance of this experiment to the effectiveness of the product was not clear to the Panel. The most important points raised were the pH of extraction, the time of extraction and the inability to detemine antigen E in the extract prior to the addition of alum.

(7) Another Dome representative reported on the immunologic effect of the administration of Allpyral™ ragweed pollen extract to six normal nonallergic volunteers. These individuals received a series of 8 weekly injections with increasing doses of Allpyral™ ragweed pollen extract, reaching a total dose of 70,000 PNU. Ragweed specific IgE and IgG antibody responses were monitored. In addition, direct skin tests and passive serum transfer (P–K) studies were performed, challenging with antigen E and whole ragweed pollen extract. The relevant data from these studies may be summarized as follows:

(i) Within 2 to 4 weeks after initial injections, all normal volunteers developed ragweed specific IgE antibody as measured by direct skin tests and P–K tests. P–K titers of at least 1:1,000 were found in all six subjects. One subject had a titer of 1:5,000. This antibody resembled spontaneously occurring specific IgE antibody. Direct skin tests also became positive in all subjects within 2 to 4 weeks after beginning the injections. Direct skin tests and P–K tests were elicited with both antigen E (0.5 mcg/mL) and whole ragweed extract.

There were other findings which did not conform to the above results. Serum antibody could not be demonstrated by RAST or by passive cutaneous anaphylaxis in monkey skin. Antigen-induced histamine release could not be demonstrated with leukocytes from any of the immunized volunteers. Curiously, for a very transient period, two of the subjects' sera were able to passively sensitize normal human leukocytes. There was no explanation for the apparent demonstration of ragweed specific IgE antibody by several techniques and failure to find it by other methods which are more sensitive.

(ii) Trace amounts of IgG antibodies specific for antigen E first appeared 6 months after the initial injections. This antibody was measured by radioimmunoelectrophoresis.

(iii) In a small double-blind clinical study conducted in 1972, patients were given Allpyral™ ragweed pollen extract or placebo (Ref. 81). In this study, there were no significant differences in RAST, leukocyte histamine release, antigen binding or passive hemagglutination tests between active and placebo treated groups. There was a suggestion that Allpyral™ ragweed pollen extract may have been clinically effective.

Critique: It is very difficult to explain the findings from the above human immunological studies. It is most unusual to find such high IgE specific antibodies in normal individuals receiving ragweed pollen extract injections. Such titers usually occur only in naturally sensitive individuals and even in such cases are usually not as high as reported. Iatrogenically induced IgE antibodies (e.g., penicillin, insulin, horse serum) are usually considerably lower in titer, even in patients who become clinically sensitive. The failure to demonstrate the IgE antibodies by other in vitro techniques such as RAST, leukocyte histamine release and passive transfer to monkey skin, raised serious doubts about the validity and interpretation of these results.

The failure to find significant IgG antibody responses in the non-allergenic recipients suggests that Allpyral™ ragweed pollen extract is relatively nonantigenic. In normal volunteers given aqueous ragweed extract, IgG antibody production is readily stimulated (Ref. 105).

Finally, one clinical study reported by Dome also suggested that Allpyral™ ragweed pollen extract is immunologically ineffective.

(8) In a summary of the presentations at the same meeting (Ref. 81), another Dome representative referred to reports by Gordon and Thompson, and Tuft and Friedman. He suggested that these reports indicated that specific antibody is induced during immunotherapy with Allpyral™ ragweed pollen extract and that these studies were important because they were presumably accomplished following the 1972 change in the methods of preparation of Allpyral™ extracts mentioned above. These papers were reviewed by the Panel with the following comments:

(i) In the paper by Gordon and Thompson (Ref. 99), an indirect immunofluorescent test using ragweed pollen grains for identification of ragweed specific antibodies was described. Sera obtained from 16 patients treated with Allpyral™ ragweed pollen extract and from 11 non-allergic control subjects were incubated with washed pollen grains. To the washed serum-pollen mix, fluorescein-conjugated antiglobulin (IgG, IgA, IgM and IgE) antisera were added. For each pollen grain, an estimate was made of the percentage of its circumference showing fluorescein staining. Three hundred consecutive pollen grains were examined and the percent labeling of each grain recorded. From this information, the mean percent of fluorescein labeling was calculated for each serum. As a control, the patients' sera were absorbed with ragweed pollen grains and then tested as described above. An unrelated pollen, red cedar, was used as another control. The authors reported finding ragweed-specific antibodies by this technique, and these antibodies were removed by absorption with pollen. Thus the technique appears to measure ragweed specific antibodies. It was stated that the treated patients had a marked rise in IgG ragweed antibodies. The data were presented in terms of mean percent fluorescence, a method which is difficult to interpret in quantitative terms. The authors failed to mention the number of patients whose serum gave evidence of antibodies. As there was no control group of patients treated with with aqueous ragweed extract, it is not possible to compare the antigenicity of Allpyral™ ragweed pollen extract with that of aqueous ragweed pollen extract therapy.

(ii) In the Tuft and Friedman report (Ref. 100), 18 ragweed-sensitive patients received injections of Allpyral™ ragweed pollen extract in doses of 6,000 to 8,000 PNU at intervals of 2 to 4 months over a 2-year period and had sequential measurement of their antibody response by the method of Gordon and Thompson. At the time the first bleeding and again at the end of 1 year of treatment, all patients but one had evidence of IgG antibodies. Over the next 12-month period, there was no change in the titer of this antibody in 12, an increase in 4, and a decrease in the sera of 2 patients. Hemagglutinating antibody was present in serum from 16 of 18 patients. Over a 1-year period, there was no change in the titer of this antibody in 12, an increase in 4, and a decrease in the sera of 2 patients. The authors interpreted these data to indicate that ragweed hay fever patients can tolerate doses of Allpyral™ ragweed pollen extract at long intervals without affecting the clinical outcome or immunological "tolerance." One might also interpret these results to show that there is very little immunological stimulation from the administration of Allpyral™ ragweed pollen extract in this manner. The Panel did not agree with the authors' claim that these data show an immunologic response associated with the administration of Allpyral™ ragweed pollen extract.

(iii) To summarize: (*a*) None of the reports on the use of Allpyral™ ragweed pollen extract, including others mentioned below, meet the criteria for adequately controlled clinical studies. (*b*) Allpyral™ ragweed pollen extract lacks detectable antigen E. This finding was verified by the manufacturer at a meeting of the Panel (Ref. 81). Therefore, the potency of this product currently cannot be determined by assay of antigen E. (*c*) There is not clear-cut immunological response to ragweed pollen allergens as measured by the production of IgG antibodies after administration of Allpyral™ ragweed pollen extract. (*d*) There is a lack of acceptable clinical studies showing the effectiveness of Allpryal™ ragweed extract.

b. Other studies of pyridine extracted alum-precipitated allergenic extracts, many submitted by the manufacturer (Ref. 16), are evaluated below. In most reports, the studies were not controlled, did not include a comparison with an aqueous extract-treated group or a placebo group, and did not contain details indicating that symptom improvements were carefully evaluated.

(1) *Other studies of pollen extracts.* According to one investigator, the rye grass I antigen may not be destroyed by the alkaline-pyridine extraction process used prior to 1972 (Ref. 20). There are no data on the effect of the currently employed extraction method on rye grass antigens. Rather low levels of serum antibodies were found following immunotherapy with Allpyral™ grass pollen (sic) extract (Ref. 25); this study was also done before 1972. Uncontrolled clinical observations suggest that Allpyral™ grass pollen extract may be effective in the therapy of grass pollen allergy.

The electrophoretic mobility and antigenicity of birch pollen extract are altered drastically by the currently used method of extraction (Ref. 101).

Sobel (Refs. 37 and 38) reported the results of uncontrolled studies with grass and ragweed pollen extracts over a period of years. The first paper related experiences in 1959 to 1963 with aqueous extracts, emulsion extracts and alum-precipitated extracts of ragweed and grass pollens administered to 902 patients. Clinical results were felt to be the same for all preparations. In the second report, using five different grass and ragweed preparations, including aqueous extracts, emulsion extracts, Allpyral™ extracts, Allpyral™ extracts in Algivant and aqueous extracts in Algivant, the preparations again were reported to be of equal effectiveness in over 2,000 patients. Good results were reported in about 63 percent of all patients. Patient evaluation was primarily subjective.

Critique: These were not controlled clinical studies, and it was not clear how patients were selected for each form of treatment. Comparison were not made in the same year; for example, aqueous treatment was compared with the results of emulsion treatment given in other years. Overall, the studies show no advantage in favor of Allpyral™ extracts.

Frankland (Ref. 39) reported in an abstract that Allpyral™ grass extract was as effective as aqueous grass extracts; however, fewer injections of the Allpyral™ extract were required. There were no details about the patient selection and evaluation critera.

Gaillard, Schellin and Mayers (Ref. 40) reported the results of uncontrolled studies with tree, grass, and ragweed pollen Allpyral™ extracts in over 600 patients. Evaluation was done by patients' subjective reports. The results were recorded as excellent in 70 percent, good in 19 percent, moderate in 8 percent, and poor in 3 percent.

Critique: There was comparison with aqueous extracts in this uncontrolled study. The evaluation of patients' response was not done with regular followup visits during the season.

Harris (Ref. 41) compared alum-precipitated pyridine extracted pollen extracts with aqeous and emulsion pollen extracts in 362 patients primarily sensitive to grass pollen. Patients apparently were taken into this study in consecutive order; it was not a controlled study. Fifty-seven patients received alum-precipitated pyridine extracts, 130 received emulsion extracts; and 173, the majority of the patients, received aqeous extracts. He concluded that alum-precipitated extracts may be somewhat better because good-to-excellent results were reported by about 80 percent of 40 previously untreated patients compared with 60 percent in 15 previously untreated patients in the aqueous extract group. Results were reported as good-to-excellent in about 80 percent of the previously treated patients in each of the three groups.

Critique: This was not a controlled study. It is not clear how patients were selected for the study and how they were assigned to one of the treatment groups. Patients apparently were not seen regularly during the pollen season. Rather, evaluation was done only at the end of the season.

Knights and Tees (Ref. 42) treated 158 grass hay fever patients. These authors reported that two alum containing preparations, Allpyral™ and Alavac ™, were not as effective as emulsified pollen extracts. Patients kept symptom cards for evaluation. These cards were reviewed at the end of the pollen season.

Critique: Patient selection was not well defined, and this was not a controlled study. Patients were not evaluated adequately.

Liebskind (Ref. 43) reported Allpyral™ grass pollen extract was as good or better than aqueous grass pollen extract in 21 highly sensitive patients who were unable to receive adequate doses of aqueous extract. These patients were able to tolerate much higher doses of Allpyral™ grass pollen extract. He reported that 17 of these patients had a good clinical response. Complicating the interpretation of this report is the fact that the Allpyral™ extract was used in a different season than the aqueous extracts.

Frankland and Noelpp (Ref. 44) treated 109 patients with aqueous grass pollen extract and 111 patients with Allpyral™ grass pollen extract. They reported approximately 90 percent good results in both groups. They believed that the advantage to Allpyral™ extracts rested in the use of fewer injections.

Critique: Selection of patients and assignment to a group were not defined, but apparently was not done on the basis of sensitivity to grass pollen. Evaluation of the patients was done only after the season, and it was based on the patients' records; patients were not examined during the season.

Mamelok (Ref. 45) reported 81 of 87 allergic patients treated preseasonally with Allpyral™ ragweed extract had good-to-excellent results. In addition, 48 patients received coseasonal treatment of the same product and also had good-to-excellent results.

Critique: Patient evaluation criteria were not defined, and this was not a controlled study. The superb coseasonal results leave some doubts concerning *this* report since there are doubts about the effectiveness of this approach to therapy using aqueous extracts.

Casgrain, Leger, and Leger (Ref. 46) reported that 100 of 127 allergic patients who received Allpyral™ ragweed extract had good to excellent results. They thought that this result was comparable to others obtained with aqueous extracts.

Critique: Patient selection and evaluation criteria were not defined, and this was an uncontrolled trial.

In a second paper, Casgrain, Leger and Leger (Ref. 47) reported very similar results following a similar study. The same critique is applicable to this study.

Munro-Ashman (Ref. 48) reported that of 160 patients receiving Allpyral™

grass pollen extract, 134 had good results. Another 51 patients received coseasonal treatment with Allpyral™ grass pollen extract, and 36 had a good result.

Critique: This was not a controlled study. Patients were not examined regularly during the grass pollen season.

DeGara (Ref. 49) treated approximately 300 patients with tree, grass, and ragweed pollen Allpyral™ extracts and reported that 80 percent had good results; similar to those found with aqueous extracts of the same pollens. Patient selection and evaluation criteria were not defined. This was not a controlled study.

In a series of four articles, Tuft and collaborators recounted the use of Allpyral™ extracts, particularly ragweed, in a large number of patients. The first paper deals with the use of tree, grass, and plantain pollen extracts and *Alternaria* extracts (Ref. 50). In this and other papers, patients were evaluated as follows: Excellent results—no more than 3 days of severe symptoms during the season; good results—3 to 5 days of severe symptoms; fair results—5 to 7 bad days; poor results—greater than 7 days of severe symptoms. Excellent-to-good results were considered as treatment successes. In the groups treated with tree, grass or plantain pollen extracts, 90 percent of the sucess rate was also 22 of 25 patients. The difficulty in assessing *Alternaria* evaluation was properly pointed out. It was not clear how the final determination of these results was made. In addition, 48 of 66 patients improved after receiving Allpyral™ house dust extract.

Critique: This was not a controlled study, and there was no comparison with aqueous extracts. The criteria for placing patients in various response categories are open to question.

Dal Bo (Ref. 51) treated 78 patents with Allpyral™ grass pollen extracts and reported 85 percent good results. However, details of the clinical evaluation were not included. There was no aqueous comparison group.

Martin (Ref. 52) treated 176 patients with Allpyral™ grass pollen extracts. Patients received an extract mixture of seven different grass pollens. He reported that the results were as good as with aqueous extracts. However, there was no control group in this study, and the details of patient selection and evaluation were not reported.

Sanders and Bachman (Ref. 53) initiated treatment of 50 grass-sensitive children with Allpyral™ grass pollen extracts. This was a double-blind study which included a saline control group. None of the patients had received previous immunotherapy. The manufacturer prepared specific extract bottles for each patient, apparently based on the initial skin test reaction, although this point was not clear in the report. Nine injections were given, with doses from 10 PNU initially to 2,400 PNU later. Injections were given by the patients' family doctor from February until April. Symptom diary cards were kept from May through July and returned in August. Patients were not examined by a physician during the study. Forty patients (80 percent) completed the study. According to the authors, 70 percent of actively treated patients compared to 45 percent of placebo treated patients had a satisfactory response. There were fewer days with symptoms in the treated group compared to the placebo-treated group. It should be noted that five patients in each group had an excellent response, while none of the allergen-treated group and four of the placebo-treated group had a good response.

Critique: No patient examinations or interviews were conducted during the grass pollen season. It was not clear whether patients in the two groups had been matched on the basis of sensitivity. There was no comparison with a group treated with aqueous pollen extract.

Sobel (Ref. 55) reported 11 years experience with ragweed extracts in a variety of forms including Allpyral™, Allpyral™ in Algivant, aqueous extract in Algivant, and emulsified aqueous extract. She concluded that the clinical results were essentially the same with all these forms. However, fewer injections of the Allpyral™ extracts were given to achieve these results.

Critique: It is not clear how patients were assigned to a particular treatment group each year. Patients were evaluated by the author as simply satisfactory or unsatisfactory. Some patients were examined; some reported by telephone; and some reported by written correspondence. To some extent, a different patient population was studied each year. Comparisons were not made with different extracts the same year.

Sobel (Ref. 72) also reported a 13-year experience with over 800 patients given five different grass pollen extracts. This report is similar to the above article. All preparations gave about the same degree of clinical effectiveness. The same critique noted above is applicable to this study.

Britton (Ref. 56) used two manufacturers' pyridine-extracted alum-precipitated mixed pollen extracts. All patients in this study had hay fever or asthma, were allergic to various pollens, and had previously received a variety of aqueous pollen extracts for 2 years, with some clinical benefit. Of over 700 patients given these aqueous extracts, all but 34 (more than 95 percent) had shown improvement. Two groups of almost 400 patients each were then treated with one or the other pyridine extracted alum-precipitated extracts; improvement was reported in only about 25 percent of the patients in each group. Britton attributed this relative lack of effectiveness to the fact that these extracts contained only allergens from five grass pollens, whereas the previously administered aqueous extracts had contained both grass and weed pollen allergens.

Critique: There were no uniform criteria for acceptance of patients into this study. Patients were not studied in a controlled fashion, nor were they studied in successive years. It is not clear how carefully patients were evaluated in terms of their symptoms.

Goor and Wuthrich (Ref. 57) treated 457 individuals with grass and tree pollinosis with either Allpyral™ extracts or another alum containing material, Suspral™ . They reported 90 percent good results in both groups. Patients were evaluated by a questionnaire at end of the season. Some patients were also interviewed, but the report did not state how many. Apparently no patients were examined during the season.

Critique: This was not a controlled study. There was no comparison with patients who were treated with aqueous extract. It is not clear how patients were selected for this study.

Gaillard, Mayers and Schellin (Ref. 58) treated 682 ragweed-sensitive patients with either Allpyral™, Allpyral™ emulsified in oil, or emulsions of aqueous extracts in oil. They reported excellent results with all three types of extracts with approximately 70 to 86 percent of the patients rated as having good-to-excellent results.

Critique: There was no comparison with aqueous extracts. It is not clear how patients were selected for this study. It is not clear how carefully patients were evaluated; patients apparently evaluated their own results. Symptom diaries were not used. Patients were not examined during the course of the pollen season and the study was not conducted in an adequately controlled fashion.

Gaillard, Schellin and Mayers (Ref. 59) also compared the results of treatment with Allpyral™ ragweed pollen extract and emulsified aqueous ragweed pollen extract. They again reported good-to-excellent results in approximately 85 percent of the patients

in both groups; good-to-excellent was defined as either no or 1-to-2 mild hay fever days during the course of the pollen season. Fewer local systemic reactions were found with the Allpyral™ extract.

Critique: Patient selection and evaluation were not described adequately. The process of evaluation left much to be desired. No comparison was made with aqueous extracts. Finally, clinical effectiveness of this degree is highly unusual in well-controlled studies of what is considered to be effective immunotherapy.

Munro-Ashman (Ref. 61) reported 5 years' experience with over 500 patients treated with Allpyral™ grass pollen extract. Eighty-eight percent of his patients has a good result. Daily symptom cards were kept during the grass pollen season, and patients were evaluated at the end of the season. Increased blocking antibody titers were described in a few patients who had received Allpyral™ grass pollen injections.

Critique: It is not clear how patients were selected or how they were evaluated during the pollen season. There was no comparison with an aqueous extract-treated group.

McAllen (Ref. 62) treated grass-sensitive patients with Allpyral™ grass pollen extract or emulsified grass pollen extract; some patients received only placebo injections. This was a double-blind study and daily symptoms cards were kept by the patients. Approximately 75 percent of Allpyral™ treated and emulsion-treated patients had good responses as compared to only 35 percent of the placebo patients. It was concluded that both allergen-containing materials were effective. No comparison with aqueous grass pollen extract was made in this study.

Ganderton, Brostoff, and Frankland (Ref. 64) treated 300 grass pollen-sensitive patients with Allpyral™ grass pollen extract. Patients kept data records and were evaluated at the end of the season. The treatment groups were comparable in terms of age, sex, and to some extent pollen sensitivity. Significant improvement was found only with preseasonal injections of grass pollen extract. There was no benefit in patients treated coseasonally with this extract, i.e., coseasonal treatment was no better than placebo injections. In this study there was no comparison with aqueous grass pollen extract, and it was not blinded.

Sullivan, Phipatanakul, and Slavin (Ref. 65) treated ragweed-sensitive patients with aqueous, Allpyral™ or both aqueous and Allpyral™ mixed ragweed pollen extracts. Patients treated with Allpyral™ alone did worse; the other two groups were improved.

This was not a controlled study. Only 8 patients received aqueous treatment alone; 30 received Allpyral™ extracts alone; and 75 received both. Some patients also dropped out of the study for reasons not given. This study only suggests that Allpyral™ ragweed pollen extract was not effective.

Tuft et al. (Refs. 66 through 68) described immunotherapy of ragweed-sensitive patients in a series of articles. In the initial study (Ref. 66), 55 ragweed-sensitive patients did as well with Allpyral™ extract treatment as patients treated with aqueous ragweed pollen extract. In another study of 272 patients (Ref. 67), 182 (67 percent) had good or excellent results, 90 (33 percent) had fair or poor results. In this study, daily records were kept by the patients, but they were later discarded because it was believed that the few which were returned did not contain sufficiently accurate information. Evaluation was therefore apparently done at the end of the pollen season, but the details were not clear. There was no concomitant control group in this study. Other studies by Tuft et al. relate very similar experiences and can be criticized for similar reasons.

Caplan and Haynes (Ref. 69) reported in a retrospective study that 326 out of 491 patients receiving Allpyral™ ragweed pollen extract had good responses as compared with 467 of 531 patients receiving aqueous extracts (66 versus 91 percent). They believed that the Allpyral™ extract was not as effective as aqueous extracts. They also pointed out that of 12 patients unable to take more than 500 PNU of aqueous extract and therefore considered to be treatment failures, all were able to take at least 10 times larger doses of Allpyral™ ragweed pollen extract. Nevertheless, 11 of these 12 patients remained as treatment failures.

Critique: This was a retrospective study and thus the two groups were not matched with respect to their sensitivity. Although this was not a controlled study, a trend was observed in two large groups of patients indicating that aqueous ragweed pollen extract was superior to the Allpyral™ extract.

Gaillard and Schellin (Ref. 70) suggested that a relatively small dose of Allpyral™ ragweed pollen extract (4,000 PNU) was as effective as a maintenance dose in the treatment of less sensitive patients but that highly sensitive patients required higher doses, such as 10,000 to 20,000 PNU, for effectiveness. They reported 85 percent good-to-excellent results in 164 patients.

Maclachlan (Ref. 71) treated 123 patients in 1965, 1966, and 1967 with Allpyral™ ragweed pollen extracts. Patients were evaluated at the end of the season. He reported 80 percent overall satisfactory results. Details of patient evaluation were not outlined, and this was not a controlled study.

Bruun (Ref. 73) treated 88 patients with Allpyral™ grass pollen extracts and reported good results in 93 percent of the patients. He felt this was equal to his experience with aqueous extracts. Details of patient evaluation were not outlined, and this was not a controlled study.

Grolnick and Pelz (Ref. 74) used the reverse passive transfer technique and were unable to show the release of any ragweed antigen after an injection of alum-precipitated pyridine extracts.

Gordon, Caplinger, Meade and Thompson (Ref. 75) evaluated Allpyral™ ragweed pollen extract in a double-blind study with 75 patients treated over 2 seasons. The injection material for each patient was prepared at Dome Laboratores. The patients were divided randomly into two groups: one group received ragweed extract plus other allergens to which they were allergic; patients in the other group were treated with ragweed pollen. In the first year of this study there was no difference in the overall results of the control and ragweed treated groups, although for days with high pollen counts there apparently was some difference. In the second year of the study there was a significant difference between the groups with the group that received ragweed allergen having fewer symptoms than the control group during the pollen season. Specific antibodies in serum from the patients were determined by a fluorescent method (described above). The results of these suggested a rise in IgG antibodies and a decrease in IgE antibodies as the result of treatment.

Critique: Patients were not assigned to the two treatment groups on the basis of their sensitivity to ragweed pollen. Patients were not seen at weekly intervals through the season but rather were evaluated primarily on the basis of symptom cards at the end of the season. The immunological data are not acceptable according to modern criteria.

Munro-Ashman, McEwen and Feinberg (Ref. 76) described increased blocking antibodies in serum of patients treated with Allpyral™ grass pollen extract. They used the patient's own skin, injecting pre-and post-treatment sera, for the measurement of "blocking antibody."

Weinstock and Starr (Ref. 25) compared leukocyte sensitivity and levels of "blocking" antibody in hay fever patients treated with Allpyral™ or aqueous grass pollen extracts. Forty previously untreated grass-sensitive patients were divided into three groups. One group received an aqueous extract of timothy grass pollen; one received Allpyral™ timothy grass pollen extract (prepared in Europe); and one group was not treated. Blood was taken before treatment, during the peak of the hay fever season, and again 4-to-6 weeks after treatment. Cell sensitivity, (ED_{50}) as measured by allergen induced histamine release, and blocking antibody levels as measured by histamine release inhibition were determined. The ED_{50} value (the amount of pollen releasing 50 percent histamine) of both the aqueous extract treated patients and the untreated patients decreased during the season, indicating a rise in cell sensitivity. Leukocytes from the Allpyral™ treatment group exhibited a lowered cell sensitivity, albeit of a very modest degree. Injections of aqueous and Allpyral™ extracts raised the level of serum blocking antibodies equally. Six months later, elevated levels were found in three of the eight Allpyral™ treated and six of the aqueous treated patients. No blocking antibody activity was found in the serum of the control patients. Only two patients, one in each treatment group, reported that they were not improved.

Critique: It is not clear whether the method used for the selection of patients assured that patients of equal sensitivity were assigned in the three groups. A definite immunological response apparently occurred in the Allpyral™ treated group.

Starr and Weinstock (Ref. 77) also reported significant clinical relief in 33 of 42 patients given Allpyral™ grass pollen extracts. Sera of these patients showed a rising titer of blocking antibody as measured by inhibition of leukocyte histamine release. In a second paper on the same study (Ref. 78), the authors found no change in leukocyte sensitivity as a result of the treatment. This was somewhat in contrast to their first study (Ref. 25).

In 1966, Zolov (Ref. 79) reported the results of treatment of 778 patients treated for 2 years with Allpyral™ tree, grass, or ragweed pollen extracts. Most patients were seen twice during the relevant pollen season. Seventy systemic reactions and 99 local reactions occurred. Good results were reported in 84 percent of the tree-sensitive patients, 81 percent of the grass-sensitive patients, and 74 percent of the ragweed-sensitive patients.

Critique: There were no control groups, and details of patient selection and clinical evaluation were not provided.

In a second paper, Zolov (Ref. 80) reported on 1,818 pollen-sensitive patients treated for 4 years. Similar results were reported, with approximately 75 to 80 percent good results in the pollen-treated patients.

(2) *Stinging insect whole body extracts.* Tuft and Torsney (Ref. 26) treated 23 patients who reported having had a generalized allergic reaction following an insect sting. Thirteen patients were previously untreated; six had had systemic reactions following injections with aqueous whole body extracts; four were receiving aqueous whole body extracts with no adverse reactions at the time they were switched to Allpyral™ insect extracts. No details were given as to the time of the previous sting in relation to the start of Allpyral™ injections or about the skin test reactivity at the onset of therapy. The results may be summarized as follows: Five of the six patients who had had a systemic reaction as a complication of treatment with aqueous extracts tolerated the Allpyral ™ extract with no difficulty. One of these individuals was restung by a bee and had no allergic reaction; his sensitivity to insects at the time of his sting was not known. The sixth patient's history was too complex to interpret accurately. One of the 13 individuals who had no previous treatment was restung and had a significant systemic reaction which was reported to be "less severe than that which occurred at first." The four remaining patients, who were receiving injections of aqueous whole body extracts with no systemic reactions, were switched to Allpyral™ extracts; two were restung subsequently and had no systemic reaction. In sum, five patients had six stings and only one of them resulted in a systemic reaction.

Critique: On the basis of current knowledge of allergy to stinging insects, the value of Allpyral™ mixed stinging insect whole body extract was not established by this study. There was no comparable group of patients treated with standardized aqueous whole body extracts and there was no untreated control group. The patients' sensitivity to insect venoms was not extablished. There were no immunological stuies. The identification of the insect causing the initial and subsequent sting was made in only three patients. Specific details of previous therapy were lacking.

Fox (Ref. 27) treated 86 patients who had reported severe systemic reactions from insect stings. All were treated with an Allpyral™ mixed insect whole body extract. Forty of these patients were stung while on therapy. One had a systemic reaction. Six were given immediate therapy for anaphylaxis, such as adrenalin, and apparently did not have an anaphylactic reaction. There was also no reaction following the sting in the remaining 33 patients although they did not receive epinephrine.

Critique: This was not a controlled study. Details of the patient's sensitivity to specific insects was not established.

Friedman and Mascia (Ref. 28) treated 48 children, who had previously had a systemic allergic reaction to a stinging insect, with Allpyral™ mixed insect whole body extract. Twenty-eight of them were stung while on treatment; one had a systemic reaction. The authors stated, "We feel that our clinical results approximate previously reported series using aqueous extracts."

One criticism of the Allpyral™ stinging insect extracts is that they are prepared from whole insect bodies, source materials which have recently been demonstrated to contain inadequate amounts of the relevant allergens, i.e., venom proteins. For a discussion of this issue, refer to the Panel review of stinging insect aqueous extracts.

(3) *Mold extracts.* Liebeskind (Ref. 29) treated 145 patients with Allpyral™ mold extracts, including *Hormodendrum, Alternaria, Aspergillus* and *Penicillium* species. He reported good results (meaning no symptoms occurred) in 81 percent of the patients, moderate improvement in 14 percent and an unsatisfactory result in 5 percent. He concluded that Allpyral™ mold extract therapy was much better than previously used aqueous extracts.

Critique: It was not clear in this report how the patients were actually evaluated nor was it clear that there was a defined mold season or exposure. Patients treated with aqueous extracts in the same year were not studied. The study was not adequately controlled.

(4) *Animal dander extracts.* Tuft and Torsney (Ref. 30) treated 40 patients with Allpyral™ animal dander extracts. Seventeen patients were treated with dog, 18 with cat, 4 with horse, and 1 with rat epidermal extract. All the patients were reported to have clinical symptoms. Of interest is the fact that 11 of the 17 dog-sensitive patients and 8 of the 18 cat-sensitive patients had only doubtful or slightly positive skin tests with the respective aqueous animal epidermal extract. They reported that

the majority of patients were improved following treatment with these extracts.

Critique. This was not a controlled study, and there was no comparison group treated with aqueous extracts. Details of exposure of the patients to animals were not given.

Brown and Wolfe (Ref. 31) treated patients allergic to animals with Allpyral™ or aqueous epidermal extracts. All patients had positive skin tests to one or more animals. In the Allpyral™ extract group, 38 were treated with dog, 27 with cat, 2 with horse and 1 with rabbit epidermal extract. In the aqueous extract group, 12 were treated with dog and 7 with cat epidermal extract. Poor clinical results were obtained with both aqueous and Allpyral™ extracts. For example, no improvement was found in 27 of the 38 patients receiving Allpyral™ dog extract or in 18 of the 27 patients receiving Allpyral™ cat extract.

Critique: Comparison was made with patients receiving different extracts at the same time. Exposure to animals was not controlled and this was not a double-blind study.

Guerin and Hewitt (Ref. 102) recently observed that extraction of cat fur with an alkaline-pyridine solution destroyed most of the allergenic material in the extract, as determined by isoelectric focussing and RAST analysis of the gel slices.

(5) *House dust extracts.* Nozik and Vinocur (Ref. 32) treated 255 patients with Allpyral™ house dust extracts. Most patients also received extracts of other allergens concomitantly. The authors reported that 26 patients had excellent responses and 201 had good responses.

Critique: Selection criteria for the patients in this study were not clearly explained. The criteria used to diagnose dust allergy were not defined. The method of evaluating the patients was not described. There was no comparison with aqueous extracts.

(6) *Reports on multiple or unspecified Allpyral™* extracts. Fagerberg, Nilzen and Wiholm (Ref. 33) treated 36 patients with Allpyral™ tree, grass and animal epidermal extracts. All patients had positive skin, nasal and bronchial provocation tests with the relevant aqueous extracts. Provocation tests done after treatment revealed reduced sensitivity in 43 of 50 patients. All but two patients were subjectively improved. Blocking antibody was found in the serum of 15 patients after treatment. Passive transfer tests with serum from several patients remained unchanged.

Critique: The details of the clinical evaluation were not given. Standardization of the provocation test was not clearly explained.

Hyde (Ref. 34) reported treating over 1,000 patients with a variety of Allpyral™ extracts. In the initial years of treatment, Allpyral™ extracts were believed to be more effective than aqueous extracts. In the last 3 years of this experience, Hyde observed a reversal of the previous pattern and stated that there was no great advantage to the Allpyral™ products. These data were presented only in abstract form. Thus, there were not enough details to permit adequate analysis of this report. As is true for most of the reports cited above, this was not a controlled study.

Cueva, Castillo and Venegas (Ref. 35) treated 60 patients with a variety of Alpyral™ extracts including house dust, pollens, and molds. Excellent results were reported in 50 patients, some improvement in another 6 patients, and no improvement in 4 patients. There was no aqueous extract control for these studies, and there were no details of patient selection and evaluation given.

Evans (Ref. 36) treated patients with Allpyral™ pollen and mold extracts and reported good results in 81 percent of the patients. These results were said to be similar to those found after previous treatment with aqueous extracts in the same patients

Critique: There was no control group treated concomitantly with aqueous extracts. Patients used diary forms to record their symptoms. However, they were evaluated only at the end of the season.

Benack (Ref. 63) treated 34 patients with asthma, rhinitis, and nasal polyps, using Allpyral™ pollen and house dust extracts. Improvement was reported in all patients. There was no aqueous extract control group. There were no details of patient selection or details of how the extracts were evaluated for effectiveness in relation to allergen exposure.

c. *Conclusions and recommendations regarding alkaline-pyridine extracted, alum-precipitated (Allpyral™) allergenic extracts*— (1) In published reports as well as in information submitted by the manufacturer, Dome Laboratories Division, there is substantial evidence that the principal allergenic components of short ragweed pollen are destroyed or altered drastically, presumably as a consequence of the alkaline-pyridine extraction, the conditions of which are known to denature proteins. Data on the antigenicity of Allpyral™ short ragweed pollen extract in experimental animals are inconclusive, and there are few data on the antigenicity of these products in humans. In addition, the ability of highly sensitive patients to tolerate much larger doses of Allpyral™ extracts than the corresponding aqueous extracts might be due to the reduced allergenicity resulting from the denaturing extraction medium. There remains the possibility that these denatured allergenic substances still might be effective in the treatment of allergic diseases; consider, for example, recent studies of the effect of formaldehyde-treated and glutaraldehyde-treated allergens.

(2) The potency of Allpyral™ allergenic extracts is not known. One study indicates that a majority of the allergen extracted from the source material is not adsorbed onto the alum used in these products. A method to quantitate the amount of allergenic extract adsorbed onto the alum must be developed so that the potency of these products can be determined accurately. Since the material that presumably is adsorbed is at least partly denatured, unique reference preparations must be developed for each Allpyral™ extract; the usual aqueous allergenic extracts are not suitable to use as reference preparations for Allpyral™ extracts. Nevertheless, comparisons with standard aqueous extracts should also be made.

(3) Because the method of manufacturing these extracts was changed significantly in 1972 (i.e., it may have been made more denaturing) some of the earlier data on clinical effectiveness may not apply to currently marketed products. In spite of numerous reports on the use of various Allpyral™ extracts in the therapy of allergic diseases, acceptable evidence for their effectiveness is still lacking. Because of the unique nature of these extracts, it is essential that some measure of their potency be obtained before evaluation of their clinical effectiveness is undertaken or the conclusions derived from such studies would be applicable only to the particular batch of the product used in a given study.

(4) Comments made earlier about the safety of alum-precipitated extracts apply as well to Allpyral™ extracts. In addition, special consideration ought to be given to the safety of these altered allergens although, based on uncontrolled clinical observations, there appears to be at least no greater risk to their use in therapy than to the use of the corresponding aqueous allergenic extracts.

(5) The Panel recommends that Allpyral™ short ragweed pollen extract should be placed in Category IIIB, because the bulk of the evidence cited above suggests that this extract is not

effective. Allpyral™ extracts corresponding to aqueous extracts which the Panel recommended for Category IIIB should also be placed in Category IIIB. This includes whole body winged *hymenoptera* extracts for insect sting allergy and wool extract.

With respect to all other Allpyral™ allergenic extracts (including rye grass pollen extract, about which there is some evidence supporting its effectiveness), the Panel recommends that: (a) Because evidence is accumulating that the currently used alkaline-pyridine extraction process greatly alters the immunologic properties of the components of allergenic extracts, (b) because potency cannot be determined accurately either with aqueous extracts as reference preparations or by known correlation with clinical improvement and (c) because the evidence supporting their effectiveness is equivocal (with the possible exception of rye grass pollen extract, as noted above), all other Allpyral™ extracts should be placed in Category IIIA for an initial period of 2 years. During this time, the manufacturer should obtain and submit evidence bearing on the ability of a substantial number of these extracts to induce specific antibodies of the IgG class in humans and should also demonstrate that these antibodies are specific for one or more of the principal allergens in the corresponding extract. In addition, the manufacturer must also have developed a method to ascertain the potency of these products. If within the 2 years, evidence of immunogenicity in humans is obtained and is judged substantial, then these extracts may remain in Category IIIA until the manufacturer submits evidence on the effectiveness and safety of these products for use in therapy according to the general time and clinical testing recommendations of the Panel. If evidence for the efficacy and safety of an Allpyral™ product is deemed adequate, and all other requirements are met (e.g., those related to standardization), then the respective product should be placed in Category I. If such evidence is not developed within an appropriate period, than all such products should be placed in Category IIIB pending further detailed study of their effectiveness and safety.

Should the manufacturer be unable to obtain substantial evidence for the immunogenicity of a substantial number of these products within 2 years, as recommended above, then all such products for which this evidence has not been obtained should be placed in Category IIIB, unless evidence from clinical studies demonstrates that some or all of these products are effective and safe for use in the therapy of allergenic sensitivity.

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VI. Plant Oleoresins

1. *Introduction.* Many plants have been found to produce allergic contact dermatitis in humans. The most common offenders are poison ivy and poison oak. Under most circumstances the dermatitis is caused by plant oleoresins which in appropriate concentrations are not primary irritants but are true allergens which produce contact dermatitis only in subjects with specific delayed hypersensitivity or cellular immunity (Refs. 1 and 2).

Plants in natural form contain varying amounts of the oleoresins. In addition, they may contain other chemicals which may be primary irritants when applied to the skin (Refs. 1, 2, 17, and 22). It is therefore, necessary to extract the oleoresins from the plants so that a potent and relatively pure immunologic substance is available for diagnostic patch testing or immunotherapy (Refs. 2 and 22).

Table 1 below lists the plant oleoresins submitted to the Panel for review of safety, effectiveness, and proper labeling for patch test diagnosis and immunotherapy. The Panel recommends that more precise labeling be used to identify the species of the plant serving as the source of each oleoresin. For example, primrose includes many species, some of which are nonallergenic. The common allergenic species is *Primula obconica* (Refs. 3 and 4). Table 1 also lists the Panel category recommendations for use in patch testing and in oral immunotherapy for those generic substances which meet potency standards.

2. *Manufacturing method.* Plants used in the preparation of oleoresins must be collected by personnel who can assure botanical identity and homogeneity. Careful attention to species may be important. For example, the primrose *Primula obconica* contains primin and is sensitizing, whereas other species such as *Primula malacoides* do not contain primin and are not sensitizing (Refs. 3 and 4). The plant should be harvested at a time when it contains the sensitizing substance. *Primula obconica* contains copious amounts of primin in the spring and summer, but little or none in the winter in some climates (Refs. 3 and 5).

TABLE 1.—PLANT OLEORESIN GENERIC RECOMMENDATIONS

Oleoresin	Category for potent product	
	Patch test	Oral immunotherapy
Wild plants:		
Acacia	IIIA	IIIA
Alder	IIIA	IIIA
Ash	IIIA	IIIA
Aspen	IIIA	IIIA
Aster (*Callistephus*)	IIIA	IIIB
Barnyard grass	IIIA	IIIA
Bermuda grass	IIIA	IIIA
Birch	IIIA	IIIA
Bitterweed (*Helenium tenuifolium*).	I	IIIB
Black-eyed Susan (*Rudbeckia hirta*).	IIIA	IIIB
Box elder	IIIA	IIIA
Brome	IIIA	IIIA
Buffalo grass	IIIA	IIIA
Burdock (*Arctium*)	IIIA	IIIB
Burweed marshelder (*Iva xanthifolia*).	IIIA	IIIB
Cedar/juniper	IIIA	IIIA
Cedar, salt	IIIA	IIIA
Chicory (*Chichorium intybus L.*).	IIIA	IIIB
Cocklebur (*Xanthium commune*).	IIIA	IIIB
Cottonwood	IIIA	IIIA
Crabgrass	IIIA	IIIA
Dandelion (*Taraxacum officinale*).	IIIA	IIIB
Dock, yellow	IIIA	IIIA
Dog fennel (*Anthemis cotula*)	IIIA	IIIB
Dropseed grass	IIIA	IIIA
Elm, American	IIIA	IIIA
Elm, Chinese	IIIA	IIIA
Eucalyptus	IIIA	IIIA
Fir	IIIA	IIIA
Fleabane (*Erigeron*)	IIIA	IIIB
Foxtail grass	IIIA	IIIA
Goldenrod (*Solidago*)	IIIA	IIIB
Grama grass	IIIA	IIIA
Hackberry	IIIA	IIIA
Hemlock	IIIA	IIIA
Hickory	IIIA	IIIA
Hoarhound	IIIA	IIIA
Horse Nettle	IIIA	IIIA
Ironweed (*Veronia*)	IIIA	IIIB
Italian ryegrass	IIIA	IIIA
Johnson grass	IIIA	IIIA
Kentucky bluegrass	IIIA	IIIA
Lamb's quarters	IIIA	IIIA
Little bluestem grass	IIIA	IIIA
Maple, sugar	IIIA	IIIA
Meadow fescue grass	IIIA	IIIA
Mesquite	IIIA	IIIA
Milkweed	IIIA	IIIA
Mulberry	IIIA	IIIA
Needle grass	IIIA	IIIA
Nightshade	IIIA	IIIA
Oak spp	IIIA	IIIA
Olive	IIIA	IIIA
Orange tree	IIIA	IIIA
Orchard grass	IIIA	IIIA
Pecan	IIIA	IIIA
Pepper tree	IIIA	IIIA
Pine spp	IIIA	IIIA
Poison ivy (*Toxicodendron radicans*).	I	I
Poison oak (*T. diversilobum*)	I	I
Ragweed, false (*Franseria acanthicarpa*).	IIIA	IIIB
Ragweed, giant (*Ambrosia trifida*).	IIIA	IIIB
Ragweed, short (*A. artemisiifolia*).	I	IIIA
Ragweed, western (*A. psilostachya*).	IIIA	IIIB
Redtop grass	IIIA	IIIA
Rough pigweed	IIIA	IIIA
Russian thistle	IIIA	IIIA
Sagebrush (*Artemesia tridentata*).	IIIA	IIIB
Saltbush (*Atriplex*)	IIIA	IIIA
Sneezeweed (*Helenium microcephalum*).	I	IIIB
Sprangletop grass	IIIA	IIIA
Spruce	IIIA	IIIA

TABLE 1.—PLANT OLEORESIN GENERIC RECOMMENDATIONS—Continued

Oleoresin	Category for potent product	
	Patch test	Oral Immunotherapy
Sweet clover	IIIA	IIIA
Sycamore	IIIA	IIIA
Threeawn grass	IIIA	IIIA
Timothy grass	IIIA	IIIA
Velvet grass	IIIA	IIIA
Walnut, black/English	IIIA	IIIA
White, sweet-clover	IIIA	IIIA
Wild barley grass	IIIA	IIIA
Wild feverfew (*Parthenium hysteroporus*).	IIIA	IIIA
Wild oats	IIIA	IIIA
Wild parsnip	IIIA	IIIA
Willow	IIIA	IIIA
Witch grass	IIIA	IIIA
Wormwood (*Artemesia absinthium*).	IIIA	IIIB
Yarrow (*Achillae lanulosa*)	IIIA	IIIB
Domesticated plants:		
Asparagus		
Cabbage	IIIA	IIIA
Blue myrtle	IIIA	IIIA
Cantaloupe	IIIA	IIIA
Carrot	IIIA	IIIA
Celery	IIIA	IIIA
Chrysanthemum (*Chrysanthemum x-morifolium*).	I	IIIB
Coreopsis (*Coreopsis*)	IIIA	IIIB
Corn	IIIA	IIIA
Corn flower	IIIA	IIIB
Cosmos (*cosmos*)	IIIA	IIIB
Dahlia (*dahlia*)	IIIA	IIIB
English ivy	IIIA	IIIA
Fern	IIIA	IIIA
Feverfew (*Chrysanthemum parthenium*).	IIIA	IIIB
Forsythia	IIIA	IIIA
Gaillardia (*gaillardia*)	IIIA	IIIB
Geranium	IIIA	IIIA
Hollyhock	IIIA	IIIA
Honeysuckle vine	IIIA	IIIA
Iris	IIIA	IIIA
Jonquil/daffodil	IIIA	IIIA
Larkspur	IIIA	IIIA
Lettuce (*Latuca sativa* L.)	IIIA	IIIB
Marigold (*tagetas*)	IIIA	IIIB
Morning glory	IIIA	IIIA
Parsnip	IIIA	IIIA
Petunia	IIIA	IIIA
Philodendron	IIIA	IIIA
Primrose [1]	I	IIIA
Privet	IIIA	IIIA
Shasta daisy (*Chrysanthemum maximum*).	IIIA	IIIB
Snapdragon	IIIA	IIIA
Snowball	IIIA	IIIA
Spinach	IIIA	IIIA
Spirea	IIIA	IIIA
Stock	IIIA	IIIA
Sunflower (*Helianthese*)	IIIA	IIIB
Tansy (*Tanacetum vulgare* L.)	IIIA	IIIB
Tomato	IIIA	IIIA
Turnip	IIIA	IIIA
Verbena	IIIA	IIIA
Virginia creeper	IIIA	IIIA
Yellow Jasmine	IIIA	IIIA
Other Oleoresins:		
Cheeses	IIIA	IIIA

[1] Primrose oleoresin has been off the market since 1974.

The leaves and stems of the plant are usually air dried and cut into small pieces. They are then extracted with a fat solvent (Ref. 2). Ethyl ether (Refs. 2 and 5), ethy alcohol (Refs. 36 and 37)and acetone (Ref. 6) have been used with satisfactory results for various plants. The nature of the fat solvent can be important for extracting the oleoresins from a particular plant. Howell has shown that poison ivy oleoresin is more soluble in ether and acetone than in ethyl alcohol and carbon tetrachloride and that ether or acetone extractions produce extracts which are 5 to 10 times more potent than those produced by absolute alcohol or carbon tetrachloride (Ref. 6). The extract is separated from the solids and concentrated by evaporation of the solvent (Ref. 2). The residual oleoresin is diluted in a solvent for use for patch testing or immunotherapy. Solvents for patch testing materials may include acetone (Refs. 2, 12, and 57), ethyl ether (Refs. 2 and 5), ethyl alcohol (Refs. 36 and 37), petrolatum (Refs. 1 and 11), corn oil (Refs. 6, 17, and 23), sesame oil (Ref. 10), or olive oil (Ref. 10). Solvents for oral therapy materials may include corn oil (Refs. 2 and 7), sesame oil (Ref. 20), or olive oil (Refs. 8 and 9). There is evidence that some plant oleoresins diluted for use in acetone, petrolatum, or corn oil will remain stable for at least 1 year if kept in tightly stoppered bottles in a refrigerator at 4° plus or menus 3 °C (Refs. 1, 23, and 24).

3. *Labeling.* The labeling should conform to the principles outlined elsewhere in this report. The common and botanical name of the plant, diluent, dilution, and storage temperature should be clearly marked on each container lable.

4. *Safety*—a. *Safety of patch testing with plant oleoresin*—(1) *Sensitization of nonsensitive patients or medical workers.* Some plant oleoresins are strong sensitizers. It is generally accepted that sufficient contact with the oleoresins of *Primula obconica* and poison ivy or oak will sensitize most or all individuals (Refs. 14, 15 and 16). It has been repeatedly shown that patch testing nonsensitive individuals can sensitize them to these oleoresins (Refs. 1 through 3 and 16). Some Oleoresins such as poison ivy and ragweed occur frequently in nature. Hypersensitivity can be a severe problem for the very sensitive patient who may find the plants difficult to avoid (Refs. 1 through 3). Therefore, medical workers applying oleoresins should be careful to keep them off their skin, and patients should not be patch tested without need. Concentrations used for patch testing should be a level which has been shown to rarely sensitize when applied for patch testing, which is the 1:10 v/v concentration or less. Shelmire (Ref. 2) used oleoresin extracts closely related to those commercially available today. Eleven volunteers, previously proved by patch testing to be nonsensitive to poison ivy, were tested daily for 6 weeks with the 1:10 v/v dilution of ivy extract. Fourteen patients, proved nonsensitive to the weeds of this series, submitted similarly to patch tests every day to every third day for a period of 2 months with extracts of the seven most sensitizing weeds. No evidence of induced sensitization was observed in any of these volunteers. Twenty-eight new born babies were tested with the 1:10 v/v ivy extract and tests were repeated 23 days later. No positive reactions were observed following either testing. Shelmire stated that: "I believe that testing with the 1:10 dilutions of a plant extract constitutes no greater exposure than the patient experiences in his routine work." Notwithstanding, he had seen patients sensitized by skin testing with 1:10 poison ivy extract but not by the other plants in his weed series (listed in a table which is included with his reprints, but not in the published article).

(2) *Local and systemic allergic reactions.* Patch testing with plant oleoresin may cause severe local or systemic contact dermatitis or cause a flareup of existing contact dermatitis due to that oleoresin (Refs. 1, 2, and 9). Patch testing is best avoided until contact dermatitis has healed (Refs. 1, 2, and 9).

(3) *Primary irritant reactions.* Very rarely, some oleoresins in strong concentration for patch testing may be primary irritants in some patients. Shelmire (Ref. 2) subjected 33 apparently normal persons to patch tests with the 1:1 v/v dilution of 55 weed oleoresins other than poison ivy. Five positive reactions were obtained in 1,815 (33 times 55) patch tests. These were considered irritative reactions since repeat tests with the 1:10 v/v dilution of the same oleoresins gave completely negative reactions. Forty-four apparently normal persons were tested with the 1:5 v/v dilutions of 55 weed oleoresins other than poison ivy. Four moderately positive reactions were obtained in 2,420 patch tests (44 times 55). When retests were made with the 1:10 dilution of the oleoresin, 1 very mildly positive reaction resulted which was interpreted as indicating subclinical sensitivity. The 1:10 v/v dilution of 56 weed oleoresins including poison ivy did not produce positive skin tests in apparently normal subjects. The oleoresins were extracted with ether by a method similar to the current commencial processes. Therefore, either 1:10 or 1:20 v/v dilutions of most plant oleoresins are used for routine patch testing.

b. *Safety of oral immunotherapy with plant oleoresins for prevention of plant oleoresin contact dermatitis*—(1) *Local and systemic allergic reactions.* Oral prophylactic immunotherapy with plant

oleoresins is adjusted to the tolerance of the patient to avoid local and systemic reaction.

Local reactions include lip dermatitis (Ref. 23), gastrointestinal reactions (Refs. 1, 17, and 23), pruritis ani (Refs. 1, 17, and 23), and pruritis vulvae (Ref. 4). Reactions about the mouth can be avoided by putting the therapeutic oleoresin dilution in a capsule (Ref. 17). Local reactions about the anus can be minimized by careful washing of the anal area with soap and water after defecation to remove residual oleoresin (Ref. 17).

Systemic reactions include erythema, urticaria, dermatitis, and exacerbation of existing clinical dermatitis or positive patch test (Refs. 1, 17, and 23). Unusual systemic reactions are pulmonary infiltrates with eosinophilia (Loeffler's syndrome) (Ref. 19), and nephritis (Ref. 18).

Careful attention to beginning treatment at a dose tolerated by the patient and increasing the dose carefully within the tolerance of the patient is required to reduce the incidence of these reactions.

(2) *Toxic reactions.* The active principles in *Compositae* oleoresins are sesquiterpene lactones. Sesquiterpene lactones have a variety of biological activities other than their allergenic activity, and some are toxic to animals (Ref. 58). Therefore, products containing sesquiterpene lactones should not be administered for oral therapy prior to establishing their safety. Until the safety problem is resolved, these substances should be limited to diagnostic use by contact skin testing. All oleoresins in this group have been recommended for Category IIIB with the exception of short ragweed for which there are several studies in which toxicity is not a problem.

c. *Safety of injection immunotherapy.* Severe local reactions occur at the sites of injection when sufficient oleoresin is given to produced satisfactory immunity (Refs. 17, 20, 21, and 22). Therefore, this form of immunotherapy is contraindicated.

d. *Safety of immunotherapy for treatment of existing plant oleoresin contact dermatitis.* Severe local and systemic reactions may occur when plant oleoresins are given either orally or by injection for treatment of existing allergic contact dermatitis (Refs. 16 and 23). The effectiveness of such therapy has not been established by controlled studies (Refs. 16, 23, and 78). Other less toxic forms of treatment are effective (Ref. 1). Therefore, immunotherapy with plant oleoresins is not recommended for treatment of existing plant oleoresin contract dermatitis.

5. *Standard of potency.* Chemical standards of potency are available for only a few plant oleoresins.The potency of poison ivy and oak oleoresins can be determined by measuring their urushiol content (Refs. 16 and 22). Suggested assay methods are available from the National Center for Drugs and Biologics of FDA. It is generally agreed that patch testing with 2 micrograms of urushiol is the equivalent of clinical exposure to the leaves of poison ivy or poison oak (Ref. 22). The potency of the oleoresins of the sensitizing primrose *Primula obconica* can be assayed by measuring its primin content by gas chromatography (Ref. 5).

It is possible that the potency of some *Compositae* oleoresin extracts can be measured by determining their content of various sesquiterpene lactones. The Panel recommends that work in this area be encouraged. The subject is discussed in more detail in the sections on specificity and the *Compositae* oleoresins.

The potency of other plant oleoresins must be measured by patch testing at the present time. Their ability to produce positive patch tests in specifically sensitive individuals and negative patch tests in normal controls should be compared to a reference standard of established potency. The volume of oleoresin per volume of diluent should be used as the labeling potency statement. Reference materials of established potency should be made available through FDA. A list of persons with known sensitivity to various oleoresins should be maintained to facilitate testing of various lots of oleoresin. There seems to be little risk to patch testing known sensitive individuals at monthly intervals to 1:10 v/v concentration of plant oleoresins, provided that this concentration has been well tolerated in the past and there is no active dermatitis at the time of testing (Ref. 2). Patch testing of controls should be done sparingly, and only one time in each person to avoid sensititization.

6. *Specificity.* Allergic sensitivity to a plant may be restricted to a single botanical species, or it may extend to related species in the same genus and to other genera in the same familiy, or it may even be confined to one or a few horticultural varieties of certain common garden plants (Ref. 38). There is considerable evidence indicating that the important allergens in plant oleoresins are single simple chemicals or a series of related chemicals which may be shared completely or in various combinations by a number of plant oleoresins. This phenomenon permits the grouping of some plant oleoresins into the families which are discussed below. However, it is important to remember that, with the probable exceptions of poison oak and poison ivy oleoresins which can be used interchangably, each of the various plant oleoresins shown in Table 1 is specific and where properly made and potent is the appropriate agent for patch test diagnosis and prophylactic oral immunotherapy of the allergic contact dermatitis caused by that particular plant oleoresin. For this reason, the availablity of a large number of plant oleoresins is desirable.

a. *Anacardiaceae family (cashew family).* This family includes poison ivy and poison oak which have been the most extensively studied. Urushiol is the name given to several pentadecylcatechols which have been isolated and identiied as the active allergens responsible for the dermatitis associated with the plants (Ref. 16). Epstein has shown that 2 micrograms of urushiol applied to the skin will produce a reaction in a sensitive subject equivalent to that produced by fresh poison oak leaves (Ref. 22). Population surveys in the United States have revealed an incidence of clinical sensitivity which is close to 50 percent (Ref. 1). Patch test screening of volunteers with 2 micrograms of urushiol produced 40 percent reactors (Ref. 22).

The pentadecylcatechols present in the other plants shown in Table 3 are closely related to the urushiol present in poison oak and poison ivy, and corss-react with them (Refs. 1 and 16) and with other phenolic compounds such as resorcinol, hexylresorcinol, and hydroquinones, but not with phenol (Refs. 16 and 31).

b. *Compositae family (daisy family).* Plants in this large family are the source of many of the oleoresins listed in Table 1 including aster, bitterweed, black-eyed Susan, burdock, burweed marshelder, chicory, cocklebur, dandelion, dog fennel, fleabane, *Gaillardia*, goldenrod, ironweed, false ragweed, giant ragweed, short ragweed, sagebrush, sneezeweed, wild feverfew, wormwood, yarrow, chrysanthemum, coreopsis, corn flower, cosmos, dahlia, feverfew, lettuce, marigold, shasta daisy, sunflower, and tansy. Cross-reactions between oleoresins from various members of the *Compositae* family are often observed, but the pattern varies from patient indicating both individual and shared antigens (Refs. 7, and 26 through 29).

At one extreme, a patient may have contact sensitivity which is confined to a single horticultural variety (cultivar) of one species of the chrysanthemum of florists, *Chrysanthemum morifolium*

(Ref. 38). At the other extreme, the patient may have contact sensitivity to a large number of *Compositae* particularly those in the related tribes *Heliantheae, Helenieae,* and *Anthemideae,* and much less commonly to the *Cynaeae, Eupotorieae,* and *Astereae* (Ref. 39).

Patients with positive patch test reactions to the oleoresins of short ragweed often, but not invariably, have positive patch test reactions to the oleoresins of other members of the *Compositae* family.

Fisher (Ref. 7) reported that of 18 proven cases of ragweed dermatitis with positive patch tests to ragweed oleoresin, 18 had positive patch tests to pyrethrum oleoresin, 4 to chrysanthemum, 4 to cocklebur, 6 to turpentine, and none to sheep sorrel, hickory, buckhorn (plantain), Kentucky blue grass, red top, orchard grass, timothy, or oak oleoresins. While all 18 patients with ragweed dermatitis reacted strongly to pyrethrum, only 3 of 8 pyrethrum-sensitive patients reacted to ragweed oleoresin.

Patients with proven cases of short ragweed contact dermatitis and positive patch tests to ragweed oleoresin have been noted to have an increased incidence of positive patch tests to pyrethrum (feverfew, or *Chrysanthemus parthenimum*) (Refs. 7, and 26 through 28), chrysanthemum (or *Chrysanthemum hortorum*) (Refs. 7 and 27), burweed marshelder (Refs. 12, 28, and 29), cocklebur (Refs. 7 and 28), bitterweed (Species not identified) (Ref. 26), false ragweed (Ref. 28), western ragweed (Ref. 29), common wormwood (Ref. 28), and sneezeweed (Ref. 28).

Sesquiterpene lactones have been found in the oleoresins of various members of the *Compositae* family (Ref. 42) and are considered responsible for the contact dermatitis caused thereby (Ref. 30). The presence of an alpha-methylene group exocyclic to the gamma lactone appears to be the immunochemical requisite for such dermatitis (Ref. 30). There are at least 600 cross-reacting allergenic sesquiterpene lactones distributed in the *Compositae* family (Ref. 31). *Frullania* or liverwort, a plant phylogenetically distant from the *Compositae,* also contains sesquiterpene lactone antigens which will cross-react with those of various *Compositae* (Refs. 32 through 34).

c. *Primula obconica* is the allergenic species of primrose, and its allergenicity depends on its content of primin (2-methoxy-6-n-pentyl-p-benzoquinone) (Refs. 5 and 13). Patients sensitive to primin may also be sensitive to related quinones, including rosewood extract (Refs. 3 and 25) and certain synthetic quinones with side chains in the 5 or 6 position (Ref. 25).

7. *Effectiveness for patch test diagnosis.* Allergic contact dematitis from plant oleoresins is a delayed type of hypersensitivity or cellular type of immune response. The clinical condition may be reproduced under controlled conditions by applying the oleoresin to the skin for 24 to 48 hours or longer through use of the open or closed patch test (Ref. 1).

a. *The open patch test.* This employs the adhesive character of the oleoresin to bind the allergen to the skin. The oleoresin is applied to the skin in a volatile vehicle, which is usually acetone. A drop of the solution is applied to the skin. The solvent evaporates leaving the oleoresin adherent to the skin. The location of the oleoresin can be identified by placing it in a predetermined place on the skin which has been marked by a grid. The natural color of the oleoresin marks the point of contact. The open patch test is easily and quickly applied. Shelmire reported routinely applying 60 tests in 5 minutes (Ref. 2). It is a less sensitive test than the closed patch test. Patients who have a positive reaction to closed patch test may have a negative reaction to open patch testing (Refs. 1 and 11). But when suitable 1:10 v/v concentrations are applied, it may reproduce the clinical exposure well, and, therefore, be suitable for screening. The small amount of contact with 1:10 v/v concentration by this method involves low risk of sensitization, similar to that obtained by natural exposure (Ref. 2).

b. *The closed patch test.* The oleoresin is applied to the skin diluted in volatile solvents such as ether (Ref. 5) or acetone (Refs. 7 and 12), or nonvolatile solvents such as petrolatum (Refs. 1 and 11), corn oil (Ref. 24), olive oil (Refs. 9 and 10), or sesame oil (Refs. 9 and 10) and covered with nonsensitizing cloth or filter paper which is secured by adhesive plaster. The location of the patch test is clearly marked by the position of the cover. Skin reactions to the cover and adhesive plaster due to sweat retention, primary irritation, and delayed hypersensitivity must be carefully distinguished from skin reactions to the oleoresin by the use of appropriate controls (Ref. 1). The closed patch test is usually more sensitive than the open patch test (Ref. 11), but not in the case of primin (Ref. 13).

c. *Interpretation of patch tests.* The patch test is a controlled clinical exposure to the oleoresin, and a positive response indicates that the patient is sensitized and is susceptible to symptoms of contact dermatitis should he or she be exposed to the plant from which the oleoresin has been extracted. The degree of reactions cannot be predicted from the test because the intensity of a clinical exposure cannot be quantitated. The test does predict the kind of response to be associated with an exposure of like intensity to that of the test.

d. *The ideal patch test for plant oleoresins.* The ideal test should give positive responses on the skin of patients known to be susceptible to the plant from which the test material has been extracted, and give on reaction on the skin of nonsusceptibles. Obviously, then it should be without primary irritative qualities. The test extract should be standardized in a manner so that the skin test dose can be measured through dilution to be equivalent to that present on the plant surfaces which account for the dermatitis. The extract should be stable under standard storage conditions. These ideals can be closely approached under conditions where the sensitizing chemical in the oleoresin are known, as in the case of urushiol for poison ivy and poison oak, and primin for *Primula obconica.* Individual plant oleoresins manufactured for patch test purposes should meet the criteria for the ideal test before being placed in Category I.

8. *Effectiveness for immunotherapy—*

a. *Immunotherapy for prevention of plant oleoresin contact dermatitis—*(1) *Oral immunotherapy.* There is good evidence indicating that oral immunotherapy with enough potent posion ivy or poison oak oleoresin will reduce the severity of allergic contact dermatitis caused by these plants in sensitive individuals, provided it is given for a sufficiently long period before contact (Refs. 1, and 20 through 23). Is is not known whether this diminished skin sensitivity is clinically relevant in all situations. This evidence is reviewed in the subsequent section on poison ivy and oak oleoresins.

By analogy, one would expect that similar oral immunotherapy with oleoresins from other plants shown to produce allergic contact dermatitis would be equally effective. However, adequate evidence from appropriate controlled studies to support this position is not available. Immunotherapy with some of these plant oleoresins may be essential for the high sensitive patient who continues to have dermatitis despite efforts to avoid a particular oleoresin because of occupation or because it is in the ambient air such as ragweed pollen (Refs. 1, 7, 9, and 23).

(2) *Injection immunotherapy.* There is also evidence indicating that injection

prophylatic immunotherapy with enough potent poison ivy or poison oak oleoresin will reduce the severity of allergic contact dermatitis caused by these plants in sensitive individuals, provided it is given for a sufficiently long period before contact (Ref. 20). As discussed in the section on safety of plant oleoresins, however, severe local reactions to adequate immunizing doses (Refs. 20 and 22) contraindicate this form of immunotherapy and make the equally effective and less toxic oral prophylactic immunotherapy the method recommended for approval by the Panel.

b. *Immunotherapy for treatment of existing plant oleoresin contact dermatitis.* There are no controlled studies demonstrating the effectiveness of oral or injection immunotherapy with plant oleoresins for treatment of existing active allergic contact dermatitis. Since severe local and systemic reactions can occur from this form of treatment, and other proven effective and less toxic methods of therapy are available, the Panel recommends that plant oleoresins not be used for this purpose.

9. *Recommendations.* A few plant oleoresin preparations have been shown to be sufficiently potent, stable, sensitive, and specific to be useful for skin test diagnosis of the specific contact dermatitis. By analogy, the Panel believes that the others might be similarly useful. However, published data to prove this point have not yet been found.

Posion ivy and poison oak oleoresins are the only plant oleoresins shown in Table 1 which have been shown by suitable controlled studies to be effective for oral immunotherapy of the specific plant contact dermatitis. By analogy, the Panel would expect others to be similarly useful, but has not found published data to prove this point.

Generic recommendations for patch test diagnosis and oral immunotherapy are listed in Table 1 and are discussed below for some of the specific plant oleoresins.

Further studies are recommended for patch test materials. These should include controlled studies of potency, stability, diagnostic sensitivity, and diagnostic specificity of each patch test plant oleoresin in Category IIIA.

An effort should be made to define the specific chemical or chemicals responsible for potency, analogous to urushiol for poison ivy and oak extracts and to primin for *Primula obconica* extracts. Sesquiterpene lactones of various chemical configurations and in varying combinations hold promise for serving this function for the *Compositae* family oleoresins (see section on "specificity") and work in this area should be encouraged. Since some sesquiterpene lactones are known to be toxic for animals (Ref. 58), further identification of the active principles and evaluation of the safety of the oleoresin for immunotherapy is recommended. Therefore, members of the *Compositae* family which may contain those substances were recommended for Category IIIB for therapy.

Controlled studies of prophylactic immunotherapy for each specific plant oleoresin will be time consuming, but should be accomplished so far as possible. Ragweed oleoresin should lend itself well to trails, providing safety can be demonstrated. There is an adequate reservior of patients with ragweed contact dermatitis, some of whom are unable to avoid the cause of their disease and are ideal candidates for immunotherapy. Ragweed oleoresin has been at least partially characterized in terms of sesquiterpene lactone content, so these studies might provide further insight into the chemicals that are responsible for ragweed contact dermatitis and that are important for immunotherapy.

Specific Plant Oleoresins

Poison Ivy and Poison Oak Oleoresins

1. *Introduction.* Poison ivy (*Toxicodendron radicans*) is found in nearly all parts of the United States and in Southern Canada. Poison oak (western poison oak, *T. diversiolobum*) occurs on the Pacific Coast of North America in Mexico, California, Oregon, Washington, and British Columbia (Refs. 16 and 82). Plants resembling poison oak superficially, but probably variants of poison ivy, such as Eastern poison oak (oakleaf poison ivy, *T. toxicarium*) and *T. rydbergii,* may be widely found in the United States (Refs. 16 and 82). Poison ivy and poison oak oleoresins are naturally present in resin canals located in the roots, stems, leaves, and fruit of the plants. Since the resin canals do not connect to the surface and there are no glandular appendages as in many other dermatitis-producing plants, the leaf must be bruised to produce a dermatitis (Refs. 2, 16, and 82). It is generally accepted that poison ivy and poison oak have the ability to induce a severe contact dermatitis in virtually everyone who has sufficient contact with the oleoresin (Refs. 1, 2, 14, and 16), and that once sensitive to either one, the patient will also react to the other and to other members of the *Anicardiaceae* family shown in Tables 2 and 3 below (Refs. 1 and 16). Apparently incorrect taxonomic classification of the poison ivy complex in the *Rhus* rather than in the *Toxicodendron* genus and the use of the term "Rhus dermatitis" by the medical profession has caused confusion in nomenclature. The classification described by Gillis (Ref. 82) is used in this review.

TABLE 2.—CHARACTERISTICS OF POISON TOXICODENDRON PLANTS

[Adapted from Fisher (Ref. 1)]

Names	Habitat	Leaves	Growth features
Common poison ivy (*Toxicodendron radicans*).	U.S.A., except the extreme southwest; throughout Canada.	Group of 3 leaflets; edges smooth or notched; green in summer, red in fall.	Woody, ropelike vine; trailing shrub on ground or erect without support.
Oakleaf poison ivy (Eastern poison oak) (*Toxicodendron toxicarium*).	Southeastern U.S.A., from New Jersey to eastern Texas.	Group of 3 leaflets; center leaf resembles oak leaf.	Low shrub.
Western poison oak (*Toxicodendron diversilobum*).	Pacific coast from southern California to Canada.	Group of 3 leaflets; center oak leaf and side leaflets of irregular shapes.	Upright shrub can grow into large spreading clumps 6 feet tall; in forests, becomes vine up to 30 feet tall.
Poison sumac (*Toxicodendron vernix*).	Damp, swampy areas throughout U.S.A., particularly east of the Mississippi.	Seven to 13 leaflets, arranged as pairs along a central with a single leaflet at the end.	Coarse woodish or tree, never a vine.

TABLE 3.—ANACARDIACEAE PLANTS RELATED TO THE POISON IVY GROUP

[Adapted from Fisher (Ref. 1)]

Common names	Scientific names	Distribution	Modes of contact
Mango "King of the fruits," "Apple of the tropics".	*Mangifera idica*	Hawaii, California, Florida, India, Central America, Mediterranean.	Direct—plant to skin.
Lacquer Tree	*Toxicodendron vernicifluum*	Japan, China	Wood boxes, bracelets, bar rails.
Cashew		India, Africa, Central America, East Indies.	Voodoo dolls, swizzle sticks, resins, mucilages, printer's ink, electric insulation.
Cashew Oil	*Anacardium occidentale*		
Indian marking nut, Dhobi (washerman) itch.	*Bella gutti*	India, Malaya	Laundry marking ink.

TABLE 3.—ANACARDIACEAE PLANTS RELATED TO THE POISON IVY GROUP—Continued

[Adapted from Fisher (Ref. 1)]

Common names	Scientific names	Distribution	Modes of contact
Regas tree, black varnish tree.	*Anacardium melanorrhoea*	Malay	Furniture, wood carvings.
Ginkgo tree	*Ginkgo biloba*	Southeastern U.S.A., China, Japan, Europe.	Oriental lacquer ware, stepping in seeds.

2. *Potency.* Starting at the turn of the century, many investigations directed towards isolating the active component in the plants, its preservation, and application in treatment have been carried out (Refs. 59, 61, and 62). The active substance first isolated was characterized as an oil, was ether soluble, and was an unsaturated member of an aromatic series. Isolation efforts over the past 70 years in different laboratories using different toxic plants including the Japanese lac tree have pointed to a commonality of agents in the various plants responsible for the dermatitis (Refs. 60 and 61). The basic group of substances are pentadecylcatechols, collectively called urushiol (Refs. 62 and 63). The chemical structures and molecular weights of at least four of these are known, as are their relative concentrations in the plants. The unsaturated components (mono-olefin, diolefin, and triolefin) are biologically more active than the saturated component (3-n-pentadecylcatechol) and represent 97 percent of urushiol (Refs. 35 and 71). The urushiol content of poison ivy and poison oak may be measured by thin-layer chromatography.

3. *Effectiveness for skin test diagnosis.* The Panel has found many studies of the diagnostic use of poison ivy and poison oak oleoresins in patients suspected of having poison ivy or poison oak allergic contact dermatitis.

Shelmire (Ref. 2) tested 50 proved cases of poison ivy allergic contact dermatitis with an open patch test with a 1.10 dilution of the oleoresin in ether or acetone. All had a typical positive reaction. He stated:

> In the routine testing of patients clinically and subclinically sensitive to poison ivy with the 1:10 dilution of the oleoresin I have never failed to obtain a frankly positive patch reaction. Conversely, I have never encountered a positive reaction with this dilution when testing persons proved nonsensitive. Since the 1:10 dilution of the crude plant extract does not act as an irritant yet never fails to evoke reactions in both clinically and subclinically sensitive persons, this was the dilution chosen for routine patch testing.

Negative patch test reactions in 48 medical students were reported. Shelmire prepared the oleoresins used for the tests by ether extractions of finely ground dried poison ivy leaves.

Shelmire (Ref. 24) described patients who showed mild reactions to closed patch tests with 1:100 dilution of poison ivy oleoresin in corn oil but had negative or very weak reaction to crushed poison ivy leaf. Twenty clinically sensitive patients reacted to 1:1,000 dilution or less by this closed patch test method (Ref. 24).

Kligman (Ref. 16) performed quantitative patch testing of a group of 11 poison ivy sensitive subjects with serial 10-fold dilutions of pentadecylcatechol (PDC) and poison ivy oleoresin in acetone. All subjects reacted to both preparations. On a weight-for-weight basis, the titer (greatest dilution still giving a reaction) of the oleoresin was generally 10 times (1 ten-fold dilution) greater than that for the saturated synthetic PDC. Kligman attributed the greater potency of the natural antigen to the preponderance of the more antigenic unsaturated olefins. Kligman further established that all patients who reacted to 1:10,000 PDC invariably reacted to crushed leaves, and were clinically sensitive as well. Of 463 quantitatively patch tested persons, 74 percent reacted to at least 1:100 PDC, but only 47 percent of the total were leaf-sensitive. Those who reacted to 1:100 PDC and not to leaves were presumed to have had a previous immunologic experience with the plant, and about one-third of these subclinical reactors insisted that they had had poison ivy dermatitis in the past. Kligman reported that nonallergic patients failed to react to crushed leaves, oleoresin, and 1 percent PDC However, experiments of this type are hazardous because they may induce sensitivity to poison ivy.

Auerbach and Baer (Ref. 71) studied 27 volunteers who considered themselves sensitive to poison ivy. All but one had a positive patch test reaction to 16 micrograms or less of poison ivy oleoresin, prepared by the authors by ether extraction of poison ivy leaves and applied in acetone solution. The patients were also tested with PDC which appeared to have about one tenth the potency of the poison ivy oleoresin and which did not react in the skin of all patients sensitive to poison ivy oleoresin.

Johnson et al. (Ref. 35) studied 26 volunteers with a claimed history of Rhus dermatitis. Patch tests were done with each of the four catechols present in urushiol. Twenty-five reacted to diolefin, 24 to triolefin, 19 to monoolefin and only 10 to PDC.

4. *Effectiveness for immunotherapy.* Much of the data relating to efficacy of poison ivy or oak oleoresin for prevention of poison ivy or oak allergic contract dermatitis has been reported by clinicians who have not only used a wide variety of investigative protocols, but also extracts and dosage protocols. The results show a similar variation in that they extend from very good to poor (Refs. 20, 21, 59, and 64 through 77). Some extracts were effective in decreasing skin sensitivity to poison ivy or poison oak and others were not (Refs. 21, 66, 73, and 76). Uncontrolled studies reported clinical improvement without loss of skin sensitivity (Refs. 64 and 65). It is not known whether diminished skin sensitivity is relevant in all clinical situations.

More recent studies that have made provision for a potent product and high-dose schedules, and appropriate clinical controls have clearly shown that poison ivy or oak oleoresin or urushiol can decrease the sensitivity of the skin to poison ivy or oak. This was demonstrated by pre- and posttreatment patch tests and by providing protection from dermatitis induced by random exposure to the plants (Refs. 16, 20 through 22, and 35). These same studies have demonstrated that, to be effective, poison ivy or oak urushiol must be given in large doses. The patient must receive gradually increasing amounts at weekly intervals to a total of at least 300 mg of urushiol. Such doses are not tolerated parenterally without undue morbidity from local reactions (Refs. 20, 22, and 24). They are tolerated orally if given on an appropriately graduated schedule by a physician familiar with the process of adjusting dose to patient tolerance (Ref. 22).

Shelmire (Ref. 17) treated 40 poison ivy sensitive patients with oleoresin given orally. Reduction in skin sensitivity to poison ivy oleoresin as shown by quantitative patch testing occurred in all. The data suggested that an individual must ingest at least 2.0 mL of potent poison ivy oleoresin to reduce sensitivity from a clinical to a subclinical level. The oleoresin was prepared and standardized by the author presumably by the methods described in the paragraph below.

Shelmire (Ref. 24) performed a controlled study of immunotherapy with poison ivy oleoresin. He recruited 30 patients who gave a history or repeated attacks of dermatitis due to poison ivy. All had positive patch tests with poison ivy oleoresin diluted 1:100 or more. Twenty patients were treated with poison ivy oleoresin prepared by the author by ether extraction of triturated dried poison ivy leaves or root. It was potent enough to produce a positive reaction on the back of a person of average sensitivity when diluted at least 2,500 times with corn oil and applied as a patch test. Patients were given a 1:25 or 1:10 dilution of poison ivy oleoresin in corn oil in slowly increasing oral doses to a total of 30 cc of either dilution over a period of 2 to 7 months. Pretreatment and posttreatment quantitative patch tests demonstrated that varying degrees of reduction of cutaneous sensitivity followed ingestion of the specific oil. Ten patients were kept as untreated controls; no reduction in the level of sensitivity of the skin occurred in these untreated patients.

Kligman (Ref. 20) treated 18 patients highly sensitive to poison ivy and poison oak with 8 to 10 weekly 1.0 mL injections of a placebo composed of sesame oil. Posttreatment patch tests with pentadecylcatechol (PDC) showed no decline in sensitivity. But 16 of these patients reported a satisfactory result; 7 had no dermatitis at all; and 9 had trival eruptions thereafter. Kligman reported these results as illustrative of the difficulty in assessing the results of immunotherapy except by quantitative patch testing before and after treatment in treated and control patients. Eight moderately sensitive patients were treated with intramuscular injections of poison ivy/poison oak oleoresin diluted in seasame oil. The threshold amounts that produced a decrease in skin sensitivity to PDC were 600 to 800 mg of oleoresin; maximum reduction in sensitivity required 2,000 to 2,500 mg given over 5 to 9 months and by never less than 22 injections. All had some relief in sensitivity; only one patient became completely immune to challenge by a crushed poison ivy leaf. Forty-six patients sensitive to poison ivy leaves were treated with intramuscular injections of PDC. The threshold amounts that produced a decrease in skin sensitivity to PDC were in the range of 800 to 1,100 mg: maximal results were obtained with 2,500 to 3,000 mg. A larger amount of PDC than oleoresin was required for maximal decrease in skin sensitivity. This difference was attributed to the presence of biologically more potent unsaturated allergens in the oleoresin. Six moderately sensitive patients received six injections of alum-precipitated pyridine extracts (Aqua Ivy™) according to the schedule of Passenger, et al. There was no decrease in skin sensitivity. Nine patients received treatment with poison ivy/poison oak oleoresin given orally. A definite decrease in skin sensitivity to PDC became apparent when they had received 1,000 to 1,200 mg: maximal results were obtained with 2,500 to 3,000 mg. No subject became completely immune. Sixteen patients received similar treatment with oral PDC. Significant reduction in skin sensitivity to PDC occurred after 1,500 to 1,800 mg: maximum effect occurred after 3,500 to 4,000 mg. Maximal hyposensitization endured for about 4 to 6 weeks after oral immunization, and about 8 to 10 weeks after intramuscular immunization. Local and systemic reactions were more severe after intramuscular than oral therapy and decrease in skin sensitivity was similar with both. The oral route therefore was recommended.

Kligman (Ref. 79) treated 58 *Rhus*-sensitive patients with cashew nut shell oil orally. Thirty-five hundred to 4,000 mg were needed to produce maximal decrease in skin sensitivity to PDC. He felt that the results of this study indicated that cashew nut shell oil, which is relatively inexpensive and obtainable in large amounts, could be substituted for PDC of poison ivy/poison oak oleoresin. The cashew nut shell oil was shown to produce positive patch test reactions in poison ivy/poison oak sensitive patients.

Epstein et al. (Ref. 22) treated patients who had positive patch tests to 25 micrograms or less of urushiol. In one experiment, 32 received either urushiol or placebo orally in double-blind fashion. Patch tests were repeated during and after treatment to determine the effects of therapy. Variable amounts of urushiol were given up to a total of 100 to 677 mg over a period of 3 to 23 months. Thirteen of the 16 patients receiving urushiol showed decreased responses to patch tests with urushiol, while 7 of the 13 patients receiving placebo had decreased responses to urushiol. In another double-blind study, the effects of urushiol were compared to placebo and to the effects of patch testing without oral therapy. After receiving more than 250 mg of urushiol over 6 to 12 months, 6 of 9 patients showed a decrease in responses to patch tests with urushiol. One of 9 patients similarly treated with placebo, and 1 of 9 patients patch tested only for the same period of time, showed similar decrease in response to patch test with urushiol. While a total dose of 100 mg proved effective for decreasing skin response to urushiol, a dose of 200 to 250 mg was better and a dose of more than 300 mg appeared optimal. For optimal results the minimum period of urushiol ingestion appeared to be 6 months. Urushiol was prepared by the authors from poison oak leaves collected in California.

5. *Recommendations.* Recommendations are made for the generic substances in the general statement on plant oleoresins. Recommendations for specific commercial licensed biologicals follow based upon data submitted by each manufacturer (Ref. 83).

a. *Product recommendations for poison ivy and poison oak oleoresins for diagnosis of dermatitis venenata.* The products, Poison Ivy Extract, Poison Ivy-Oak Extract Combined and Poison Oak Extract, Solution for Patch Test, manufactured by Hollister-Stier Laboratories, Division of Cutter Laboratories, License No. 8, are recommended to be placed in Category IIIA. To qualify for Category I, the products must be standardized and test dosages defined based upon levels of active components shown to be capable of detecting clinical sensitivity.

a. *Product recommendations for poison ivy, poison oak and poison sumac oleoresins for treatment of dermatitis venenata.* In reviewing commercial products now available for treatment of dermatitis venenata due to poison ivy, poison oak, and other plant oleoresins, the following factors were evaluated based on the data submissions by the producers:

(1) Identification and handling of source material.

(2) The potential of the extraction method to yield the active principle in a usable form with a minimum of unwanted contaminants.

(3) Assay of urushiol content.

(4) Effectiveness data showing the company's product will alter skin sensitivity as shown by pre- and posttreatment skin challenge by adequate and well-controlled studies, preferably with a placebo.

(5) Safety data consisting of prerelease general animal safety tests prescribed by FDA.

(6) Labeling, particularly regarding the concentration of the active principle expressed in quantity per volume of assayed active ingredient.

(7) Recommended method of use (prophylactic use was considered to be acceptable only if the product was shown to meet potency and safety standards. Treatment of active disease

was judged not to be recommended (Refs. 16, 18, and 59)).

(8) Route of administration: Oral administration was judged to be acceptable only if the product meets adequate potency levels (Ref. 22). It was concluded that for an injectable product to qualify, the company must show data that its product is both safe and effective when given by injection. As stated earlier in the general statement on Plant Oleoresins, evidence of effectiveness for administration by the injection rout was inadequate, and safety of potent injectable products is questionable.

The individual poison ivy, poison oak, and poison sumac products licensed to each manufacturer were reviewed for the above elements. Generally, the producers supplied information indicating that the first, second, and fifth criteria listed above were capable of being handled in a satisfactory manner. The identification and collection of the source materials seemed to be adequate. The methods of extraction were somewhat different from firm to firm and may be expected to result in varying yields of active oleoresins, and thus the concentration of the resultant extracts may vary. Methods of separation and concentration of the oleoresins are employed, usually followed by measured dilution to arrive at the marketed dosage form. The required FDA general safety tests in animals are performed.

Effectiveness and safety data are discussed generically in the general statement on Plant Oleoresins. Because there are no required potency assays or established potency levels, the relationship of the activity of the marketed products to those employed in the few well-controlled studies is not known.

(1) *Oral products.* None of the orally administered products have been shown to match the potency of the research materials used in one study (Ref. 22) demonstrating effectiveness for standardized urushiol-containing products in oral prophylaxis. The Panel made the following recommendations for poison ivy and poison oak products for oral use:

(a) Poison Oak Extract (ImmunOak™) oral liquid and Poison Ivy Extract (ImmunIvy™) oral liquid, manufactured by Riker Laboratories, Inc., License No. 372, Category IIIA.

(b) Poison Ivy-Oak Extracts (Combined) oral liquid, manufactured by Hollister-Stier Laboratories, Division of Cutter Laboratories, License No.8, Category IIIA.

(c) Poison Ivy Extract oral pills, manufactured by the Washington Homeopathic Pharmacy, License No. 392, Category IIIB. The regulations in § 601.25 (21 CFR 601.25) make no separate provision for standards of effectiveness for homeopathic drugs. FDA may wish to consider this product differently because it is a homeopathic remedy. There was no evidence of effectiveness for either prophylactic treatment or treatment of active disease. There is no assay for active ingredients. The product is highly diluted in accordance with homeopathic principles.

(d) All oral products should be assayed for urushiol content, and once a product of adequate potency is obtained, effectiveness data should be developed for the recommended dosage schedule.

(2) *Injectable products.* As discussed in the general statement on Plant Oleoresins, the Panel concluded that there is inadequate evidence of safety and effectiveness for the injectable *Toxicodendron* oleoresins. Potency appears to be too low to induce a reduced skin reactivity, and the use of higher potency products causes excessive local and systemic reactions. The following products are recommended to be placed in Category IIIB until safety, potency, and effectiveness are proven:

(a) Poison Ivy Extracts, injection in almond oil, manufactured by Parke, Davis and Co., License No. 1.

(b) Poison Ivy Extract, injection in olive oil, (Ivyol ™), manufactured by Merck Sharp and Dohme, Division of Merck and Co., Inc., License No. 2. At the request of the manufacturer, this product license was revoked December 6, 1978.

(c) Poison Ivy Extract, Poison Oak Extract and Poison Ivy-Poison Oak Extracts (combined), injections in alcohol, manufactured by Hollister-Stier Laboratories, Division of Cutter Laboratories, Inc., License No. 8.

(d) Poison Ivy Extract, injection in hydro-alcoholic solution (Rhustox Antigen ™), manufactured by Mulford Colloid Laboratories, Division of Lemmon Pharmacal Company, License No. 102.

(e) Poison Ivy-Oak-Sumac Extracts, combined, injection in almond oil, (Rhus-All Antigen ™), manufactured by Barry Laboratories, Inc., License No. 119.

(f) Poison Ivy Extract, Alum Precipitated, (Aqua Ivy ap ™), injection, manufactured by Miles Laboratories, Inc., License No. 362.

Primrose (Primula obconica) Oleoresin for Patch Testing

1. *Introduction.* Allergic contact dermatitis from the common household plant *Primula obconica* is frequent in most parts of Europe (Ref. 13). In the United States, many wholesale nurseries refuse to handle this primrose and instead sell nonsensitizing substitutes which include *Primula malacoides* and other varieties (Ref. 4). The allergen of *Primula obconica* is an excretory product found on small glandular hairs on the leaves and stems of the plant. The sensitizing substance was first isolated by Nestler in 1904, who obtained pure crystals by microsublimation of an ethyl ether extract of the leaves (Ref. 13). Bloch and Karrer established its approximate molecular formula and named it primin (Ref. 13). Schildknecht et al. found that primin is 2-methoxy-6-n-pentyl-p-benzoquinone and synthesized it (Ref. 13). Patients sensitive to primin may also be sensitive to related quinones including rosewood extract (Ref. 3 and 25) and certain synthetic quinones with side chains in the 6 or 5 position (Ref. 52). Reactions to the related substances are almost always weaker than that to primin (Ref. 25).

The allergenic content of *P. obconica* varies considerably, depending on season, the number of hours of sunshine, the method of cultivation, and the horticultural variety (Ref. 3). Primin-producing plants harvested in spring usually produce adequate yield (Ref. 5). The oleoresin may be extracted with either as described for other oleroesins (Ref. 5 and 13).

2. *Potency.* Since primin is the substance responsible for *Primula obconica* sensitivity, the potency of the oleoresin may be determined by measuring its primin content by gas chromatography (Ref. 5). Twenty-five microliters of active ether extract should contain approximately the potency of 25 microliters of primin 1:10,000 (Ref. 5).

3. *Effectiveness for skin test diagnosis.* Agrup et al. (Ref. 5) found that primula oleoresin produced positive patch tests in 10 individuals known to be sensitive to *P. obconica* and negative reactions in 20 nonsensitive controls. They tested 2,457 consecutive patients of unknown clinical sensitivity; positive reactions were obtained in 140; negative reactions were obtained in 2,317. Extract was made by the authors by extracting leaves and stems of *P. obconica* with ether and allowing the ether to dry on filter paper backed by aluminum foil. The patch test units were covered with aluminum foil and stored in a refrigerator.

Twenty primula sensitive patients were tested with test units prepared with an ether extract 3 years previously and stored in a refrigerator. At the same time patch tests

were performed with synthetic primin 1:10,000. The intensity of the reactions were approximately identical.

They found that *P. obconica* harvested in the winter might contain no sensitizing substance while that harvested in the spring was a rich source.

Fregert et al. (Ref. 13) reported positive patch tests to primula oleoresin in 23 patients with clinical primula dermatitis. These same patients had positive patch tests with synthetic primin 1:50,000. Two-hundred consecutive control patients had negative patch tests with primula oleoresin and primin in similar concentrations. The primula oleoresin was prepared and patch tested as described in the previously discussed paper (Ref. 5).

4. *Recommendations.* The reports of patch testing with *P. obconica* oleoresin indicate that a potent product is effective for patch test diagnosis of allergic contact dermatitis due to this oleoresin. However, it is important that the oleoresin contains primin. There is no indication that the formerly marketed primrose oleoresin contained primin. Should the product again be marketed, further studies should include the measurement of its primin content in addition to evaluating its safety and effectiveness.

Short Ragweed (Ambrosia artermisiifolia, A. elatior) Oleoresin

1. *Introduction.* Short ragweed oleoresin is naturally present on the leaves, stems, and pollen of short ragweed. Contact with this oleoresin will produce allergic contact dermatitis in individuals who have specific delayed hypersensitivy to it. This dermatitis is seen in patients throughout the distribution of short ragweed in North America and may be an occupational disease in farmers and linemen with much contact with the plant, and a seasonal problem to the intensely sensitive person who reacts wherever ragweed pollen or plant parts touch his skin, particularly on the face, the extremeties, and the neck (Refs. 2, 7, 9 through 12, 23, 26 through 30, 41, 43 through 47, and 50 through 52).

It is important to distinguish contact dermatitis due to allergy to ragweed oleoresin from that due to allergic and primary irritant reactions to other plant oleoresins and other chemicals (Refs. 2, 7, 9 through 12, 23, 26 through 29, 43, 45 through 47, and 52). It is also necessary to distinguish ragweed oleoresin allergic contact dermatitis from flareups of atopic eczema in a patient sensitive to the protein allergens in ragweed pollen responsible for ragweed pollen hay fever and asthma (Refs. 9, 10, 12, 43, 47, and 53). Patch testing with ragweed pollen oleoresin is used for the purpose of identifying patients who have contact dermatitis from allergy to this oleoresin. Specificity of ragweed oleoresins is discussed in the general statement on plant oleoresins.

2. *Effectiveness for skin test diagnosis.* The Panel has found many studies of the diagnostic use of ragweed oleoresin in patients suspected of having ragweed oleoresin allergic contact dermatitis.

Brown, Milford, and Coca (Ref. 43) reported two patients with clinical evidence of ragweed contact dermatitis. Both had strongly postivite patch tests to ragweed pollen oleoresin. Control studies were done in 40 individuals subject to ragweed hay fever, in 40 subject to other atopic hypersensitivity, and in 40 normal persons without individual or family atopic history. Hypersensitiveness to the oil applied with the patch technique was found in six individuals in each group.

Gay and Ketron (Ref. 44) reported one patient with clinical evidence of ragweed contact dermatitis. Patch tests were positive with ragweed oleoresin obtained from Dr. Coca and presumably that described by Brown, Milford, and Coca (Ref. 43).

Sulzberger and Wise (Ref. 45) and Pascher and Sulzberger (Ref. 46) reported two patients with clinical evidence of ragweed contact dermatitis. Both had strongly positive patch tests to ragweed pollen oleoresin obtained from Dr. A. F. Coca of the Lederle Laboratories.

Sheldon and Blumenthal (Ref. 8) reported 16 patients with clinical evidence of ragweed dermatitis. All had a 4-plus positive patch test to ragweed oleoresin in 1:1,000 or higher dilution. The oleoresin was prepared by the authors by extracting dried whole giant and short ragweed plants with ether for 48 hours and drying the extract at room temperature to obtain the oleoresin. The oleoresin was diluted in olive oil for patch testing. No patch tests in normal controls were reported.

Shelmire (Refs. 2 and 23) reported studies of plant oleoresins including short ragweed pollen oleoresin. Oleoresin was obtained by extracting the ground dried plant with ether. The ether extract was filtered and evaporated in an open vessel to obtain the plant oleoresin. This method is essentially the one used subsequently by Hollister-Stier Laboratories. The oleoresin was diluted 1:10 v/v in acetone for skin testing. Shelmire showed that this dilution would produce positive patch tests in 23 of 23 patients with clinical evidence of ragweed pollen contact dermatitis. He presents important data on patch tests in control patients for 56 plant oleoresins which include short ragweed pollen oleoresin:

One hundred apparently normal medical students submitted to patch tests with the 1:10 dilution of all the plants oils. Fifty-two positive reactions were noted at the sites tested with the ivy extract. The remaining patch tests were completely negative (5,600 tests). Fifty proved cases of poison ivy dermatitis tested with all 56 oleoresins showed frank vesiculation at the sites of the poison ivy tests but negative reactions at the remaining patch areas (2,800 tests). Thirty-seven persons with pollen hay fever or asthma but with no history of dermatitis were tested with the 1:10 dilution of all oleoresins except that of poison ivy. Not a single positive reaction occurred at any of the 2,035 test sites (55 times 37). Fifty-seven persons with proved contact dermatitis from other excitants, such as cosmetics, crude oil and chemicals, submitted to patch tests with all the oleoresins except that of poison ivy. One showed positive reactions to fleabane, camphor daisy, and prairie Froelichia on the initial test and on 3 retests with both the 1:10 and 1:20 dilution of the specific oleroesins. This person was considered subclinically sensitive to these three plants. The remaining 56 persons gave negative reactions at all patch sites (3,135 tests). One hundred and eighty-seven persons with miscellaneous dermatoses such as drug eruptions, postarsphenamine dermatitis, bacterial allergies, urticarias and eczemas of undertermined cause were similarly tested. Four mildly positive reactions were observed in 10,285 tests (187 times 55). I considered these reactions examples of subclinical sensitivity. In the routine testing of patients clinically and subclinically sensitive to poison ivy with the 1:10 dilution of the oleoresin I have never failed to obtain a frankly positive patch reaction. Conversely, I have never encountered a positive reaction with this dilution when testing persons proved nonsensitive. Since the 1:10 dilution of the crude plant extract does not act as an irritant yet never fails to evoke reactions in both clinically and subclinically sensitive persons, this was the dilution chosen for routine patch testing.

Ingraham (Ref. 27) reported three patients with clinical evidence of ragweed contact dermatitis. All had positive patch tests to ragweed oleoresin. Oleoresin was prepared by the author by extracting the dried whole plant for 24 hours with ether, filtering the extract through filter paper, and drying the extract at room temperature to obtain the oleoresin. The oleoresin was placed on small square of filter paper and applied to the skin. No control tests were reported.

Fisher (Ref. 7) reported four patients with clinical evidence of severe ragweed dermatitis. All had a strongly positive patch test to ragweed oleoresin from

Graham Laboratories (now Hollister-Stier Laboratories) diluted in 10 parts of acetone. Control patch tests were done with this same material in 100 patients with unrelated dermatoses, and "it was not found to be either a primary irritant or common sensitizer.

Fromer and Burrage (Ref. 10) reported 25 patients with clinical evidence of ragweed contact dermatitis, all of whom had positive patch tests. Similar patch tests were negative in 100 controls. The source of the ragweed oleoresin was not stated. The oil was diluted 1:1,000 probably in olive oil for initial testing. Testing was done at 1:100 and 1:10 dilutions subsequently if necessary. Low initial testing dilution was used to avoid severe local and systemic reactions.

Cohen (Ref. 47) reported two patients with clinical evidence of ragweed dermatitis. Both had positive patch tests with ragweed oleoresin. Ragweed oleoresin was prepared by the author. After pollen ws defatted with ether, the ether-soluble portion was filtered off and the ether allowed to evaporate, and the residual pollen oil was collected. The pollen oil was diluted in acetone (dilution used not stated) for patch testing.

Epstein (Ref. 12) reported 16 patients with clinical evidence of ragweed contact dermatitis. All had positive patch tests with ragweed pollen oleoresin. Patch tests were done by the open method with oleoresin obtained from Graham Laboratories (now Hollister-Stier). The concentration was not stated. Control patch tests were not reported.

3. *Effectiveness for immunotherapy.* The Panel has found two published studies which strongly suggest that oral immunotherapy with ragweed oleoresin will reduce the severity of contact dermatitis due to contact with the plant. However, as will be shown, critical controls are omitted in each study so that neither establishes proof of effectiveness in a definitive manner.

Sheldon and Blumenthal (Ref. 8) treated 14 patients with clincial evidence of contact dermatitis from ragweed oleoresin, and obtained positive patch tests with ragweed oleoresin in 1:1,000 or higher dilution. The ragweed oleoresin was prepared by the authors as described in the preceding section and diluted with olive oil. Treatment was begun with a drop of a dilution which gave a faintly positive patch test reaction. The dosage was increased slowly, and different final levels of dosage were achieved in different patients. Ten of the 14 patients reported good-to-complete relief, 2 reported fair relief, and 2 reported no relief from symptoms of ragweed contact dermatitis during the next ragweed season. By repeated quantitative patch testing, reduction in quantitative patch test reaction was observed in 2 patients. Before treatment, they reacted to the 1:100,000 dilution, and after 2 years of treatment they reacted to 1:1,000 dilution in one and to 1:200 in the other. Unfortunately, no observations were made on a control group of patients with equally severe ragweed contact dermatitis treated with placebo.

Fisher (Ref. 7) treated four patients with clinical evidence of contact dermatitis from ragweed oleoresin who had strongly positive patch test reactions to ragweed oleoresin. All had had their dermatitis in season for at least 5 years before treatment. All were treated with oleresin obtained from Graham Laboratories diluted in corn oil, which presumably is similar to the material marketed today by Hollister-Stier Laboratories. The patient started with one drop of the 1:100 dilution in a gelatin capsule and slowly increased the dose according to tolerance daily until taking 12 drops of the 1:25 dilution 2 or 3 times weekly. All four patients showed relief from symptoms of ragweed contact dermatitis during the ragweed season. Patch tests were repeated at 6-to-12-week intervals using a closed patch test to oleoresin diluted 1:10 in acetone. As the patients improved clinically, the strongly positive patch test reactions became progressively weaker, and in two cases the reactions became negative. Lapse from treatment occurred in only one patient and resulted in a clinical relapse and recurrence of patch test reactivity. Unfortunately, no observations were made on a control group of patients with equally severe ragweed contract dermatitis treated with placebo.

4. *Recommendations.* The reported results of patch testing with short ragweed oleoresin extract indicate that it is effective for patch test diagnosis of allergic contact dermatitis due to exposure to short ragweed oleoresin when a potent product is used.

The Panel has found only circumstantial evidence indicating that ragweed oleoresin extract is effective for immunotherapy, but recommends that, on the basis of its analogy to proven effective poison ivy and poison oak oleoresins, it should remain available for immunotherapy pending further testing. Reported experience has not identified a hazard from its potential sesquiterpene lactone content. Recommendations are made for the generic substances in the general statement on plant oleoresins. The licensed short ragweed oleoresin product should be placed in Category IIIA for patch test diagnosis and for oral prophylactic immunotherapy.

Chrysanthemum (Chrysanthemum x morifolium) Oleoresin

1. *Introduction.* The chrysanthemum is one of the most common causes of allergic contact dermatitis among florists and horticulturists (Refs. 36 and 37). The oleresins studies have usually been obtained from the chrysanthemum of florists. Patients with positive patch test reactions to chrysanthemum often, but not invariably, have positive patch test reactions to the oleoresins of other members of the *Compositae* family including ragweed (Refs. 7, 27, and 48), and to sesquiterpene lactones, including alantolactone (Ref. 36). Guinea pigs sensitized with *Chrysanthemum indicum* become sensitized to various sesquiterpene lactones, including alantolactone (Ref. 49). However, alantalactone has not been found in chrysanthemum (Ref. 49). Rook (Ref. 38) has summarized evidence indicating that rarely a patient may be sensitive only to a single variety or cultivar of *Chrysanthemum morifolium.*

2. *Effectiveness for skin test diagnosis.* Bleumink et al. (Ref. 36) reported six patients with contact dermatitis due to contact with chrysanthemums (*Chrysanthemum x morifolium*). All had strongly positive patch tests to chrysanthemum oleoresin diluted 1:10 in ethyl alcohol. Alantolactone diluted 1:100 in ethyl alcohol also produced positive patch reactions in these patients. Thirteen control patients had negative patch reactions to the chrysanthemum oleoresin. Chrysanthemum oleoresin was prepared and patch tested by the methods described in the paragraphs below.

Bleumink (Ref. 37) reported 15 patients with possible clinical evidence of allergic contact dermatitis from chrysanthemum (*Chrysanthemum x morifolium*). Eight of these had positive patch test reactions to chrysanthemum oleoresin. Of 104 controls with contact dermatitis thought not to be due to chrysanthemum, 1 gave 2 plus, 3 gave 1 plus, and 100 gave negative patch test reactions. The oleoresins were prepared by the authors by extracting *Chrysanthemum x morifolium* flowers and leaves with 95 percent ethyl alcohol, removing solids by centrifugation, and concentrating in a vacuum rotary evaporator. For patch testing, the solutions were diluted 1:10 with ethyl alcohol, and 10 microliters were applied to the "Scandanavian silver patch." Six out of 7 patients with positive patch

tests to chrysanthemum also had positive patch tests to 1 percent alantalactone in ethyl alcohol.

Mitchell (Ref. 48) reported one patient with clinical evidence of allergic contact dermatitis from chrysanthemum who had a positive patch test to chrysanthemum oleoresin. He also had positive patch tests to alantalactone, false ragweed, short ragweed, sneezeweed, marshelder, cocklebur tansy, wormwood, and yarrow. The source of the oleoresin is not stated.

Ingraham (Ref. 27) reported one patient with clinical evidence of contact dermatitis from chrysanthemum (*Chrysanthemum x morifolium*) who had a strongly positive patch test to the oleoresin. He was also clinically sensitive to, and had a positive patch test to, feverfew oleoresin. Extracts were prepared by the author. Flowers were extracted with ether. The extract was cleared by filtration and concentrated by evaporation. The oleoresin was placed on small squares of filter paper held in contact with the skin by adhesive tape faced with cellophane. Control tests were not reported.

3. *Recommendations.* The licensed product should be placed in Category IIIA for patch test diagnosis and for oral prophylactic immunotherapy.

Wild Feverfew (Parthenium hysterophorus) Oleoresin

1. *Introduction.* The weed wild feverfew (*Parthenium hysterophorus*) is widely found in waste ground in the United States between Florida and Texas in the South and Southwest; it is found locally, north to Massachusetts, Pennsylvania, Ohio, Michigan, Illinois, Missouri, and Kansas (Ref. 54). It has become widespread in the Poona region of the Maharashtra State on the west cost of India (Ref. 54). It has been widely accepted as a frequent cause of contact dermatitis in both the United States and India (Refs. 23, 28, and 54 through 57). Parthenin is the major sesquiterpene lactone found in *P. hysterophorus* (Ref. 57). The Panel has found no study to determine whether parthenin content could be used as a standard of potency for this extract.

Patients with positive patch reaction to *P. hysterophorus* commonly, but not invariably, have positive patch test reactions to other members of the *Compositae* family, most frequently to *Helenium, Dahlia, Iva,* and *Chrysanthemum,* and less often to many others (Ref. 57). They also frequently have positive patch test reactions to various sesquiterpene lactones, including parthenin, ambrosin, and alantalactone (Ref. 57).

2. *Effectiveness for skin test diagnosis.* French (Ref. 54) reported one patient with contact dermatitis following contact with *P. hysterophorus* who had a positive patch test to *P. hysterophorus* oleoresin. The oleoresin was prepared by the author by extracting 1 gram of dry *P. hysterophorus* leaves with 10 "volumes" of absolute alcohol to produce 1:10 oleoresin extract. The patient had a positive patch reaction to both 1:10 and 1:100 extract. No patch tests were done on normal control patients with the *P. hysterophorus* oleoresin extract.

Kahan and Grothaus (Ref. 55) reported two patients with contact dermatitis from contact with *P. hysterophorus* who had positive patch tests with *P. hysterophorus* oleoresin. One patient was patch tested with oleoresin in almond oil prepared by Dr. A.F. Coca; the other was patch tested with an alcohol extract prepared by the method of French (Ref. 54). They did not report any patch tests with their oleoresin extracts in normal control patients.

Shelmire (Ref. 2) reported that 27 of 27 patients clinically sensitive to *P. hysterphorus* had positive open patch tests to a 1:10 dilution of *P. hysterophorus* oleoresin in acetone or ether. This same dilution of *P. hysterophorus* oleoresin produced a negative reaction in control patients not allergic to *P. hysterophorus* in 100 normal medical students, 50 patients with poison ivy dermatitis, 37 patients with pollen hay fever or asthma, 57 patients with contact dermatitis due to something other than plant oleoresins, and 187 patients with miscellaneous dermatoes.

Ogden (Ref. 56) reported four patients with dermatitis following contact with *P. hysterophorus* who had positive patch tests with *P. hysterophorus* oleoresin. An alcoholic extract of *P. hysterophorus* leaf was used. Details of manufacture of extract and of patch testing were not given.

Lonkar, Mitchell, and Calnan (Ref. 57) reported 50 patients who had clinical evidence of contact dermatitis after contact with the plants of *P. hysterophorus.* All had a positive patch test reaction to *P. hysterophorus* leaf. The commercially available Hollister-Stier *P. hysterophorus* 1:10 oleoresin in acetone produced positive patch test reactions in 20 of these 50 patients. They did not report patch tests with leaves or oleoresin in nonallergic control patients.

3. *Effectiveness for immunotherapy.* The Panel has found no controlled studies which indicate that immunotherapy with *P. hysterophorus* oleoresin can reduce the severity of contact dermatitis due to contact with this plant. Authoritative publications (Ref. 23) state that oral immunotherapy with the oleoresin may be effective for this purpose, but data from controlled studies were not provided.

4. *Recommendations.* Some published patch test data (Ref. 57) with the commercially available Hollister-Stier *P. hysterophorus* oleoresin diluted 1:10 in acetone fail to establish sufficient diagnostic sensitivity, since only 20 of 50 patients clinically sensitive to the plant and patch test sensitive to the leaf reacted to patch testing with this agent (Ref. 57). On the other hand, Shelmire's data (Ref. 2) on oleoresin prepared by the same method suggest that sufficient diagnostic specificity and sufficient diagnostic sensitivity are attainable. The Panel suggests that the apparent differences in diagnostic sensitivity demonstrated by the two studies may been due to differences in potency of the oleoresin employed. Until these problems are resolved, the Panel recommends that the evidence for effectiveness of *P. hysterophorus* oleoresin for diagnosis be considered to be circumstantial. The Panel further recommends that on the basis of its analogy to other proven effective oleoresins that it be kept available for diagnostic use.

The Panel has found only circumstantial evidence indicating that *P. hysterophorus* oleoresin is effective for immunotherapy, but recommends on the basis of a potential safety hazard from its sesquiterpene lactone content that it should be available for immunotherapy only after its safety has been demonstrated.

It is recommended that the wild feverfew oleoresin product be placed in Category IIIA for patch test diagnosis and Category IIIB for immunotherapy.

Helenium Oleoresins

1. *Introduction.* Various members of the *Helenium* family are found in all of the States of the United States; in many, these plants are both abundant and widely distributed (Ref. 81). Characteristic, bitter, aromatic globules of the oleoresin are found on the leaves, stems, and flowers of the plants. Well recognized species included sneezeweed (*Helenium microcephalum)* and bitterweed *(Helenium tenuifolium),* both of which are reported to cause allergic contact dermatitis (Refs. 2, 23, 28, 48, and 81).

Sesquiterpene lactones are recognized as the allergens responsible for the contact dermatitis produced by these plants (Ref. 30). Helenalin is a major sesquiterpene lactone found in the *Heleniums* and has been reported to

show immunologic reactivity (Refs. 30 and 80). The Panel has found no study to determine whether Helenalin content could be used as a standard of potency for this oleoresin.

Patients with a positive patch reaction to *Helenium* commonly, but not invariably, have positive patch test reactions to other members of the *Compositae* family (Refs. 28, 30, and 32) and to *Frullania* (Ref. 32).

2. *Effectiveness for skin test diagnosis.* Balyeat et al. (Ref. 81) reported two cases of dermatitis after contact with *H. microcephalum* who had positive patch tests to the leaves, flowering tips, and oleoresin of *H. microcephalum.* The oleoresin was extracted with absolute ethyl alcohol. A 10-percent solution of the oleoresin in olive oil was used for patch testing.

Shelmire (Ref. 2) reported 29 patients who had clinical evidence of contact dermatitis from sneezeweed, *H. microcephalum,* who had positive patch tests to a 1:10 dilution of sneezeweed oleoresin in acetone or ether. He also reported 28 patients who had clinical evidence of contact dermatitis from bitterweed *H. tenuifolium* who had positive patch tests to a 1:10 dilution of bitterweed oleoresin in acetone or ether. This same dilution of both sneezeweed and bitterweed oleoresins produced negative reactions in control patients not clinically sensitive to these plants in 100 normal medical students, 50 patients with poison ivy dermatitis, 37 patients with pollen hay fever or asthma, 57 patients with contract dermatitis due to something other than plant oleoresins, and 187 patients with miscellaneous dermatoses. Shelmire prepared his oleoresins by ether extraction of dried, triturated *H. microcephalum* or *H. tenuifolium* leaves.

3. *Effectiveness for immunotherapy.* The Panel has found no controlled studies which indicate that immunotherapy with *Helenium* oleoresin can reduce the severity of contact dermatitis due to contact with this plant. Authoritative publications (Ref. 23) state that oral immunotherapy with both *H. microcephalum* and *H. tenuifolium* oleoresins may be effective for this purpose, but data from controlled studies were not provided.

4. *Recommendations.* The available evidence indicates that *H. microcephalum* and *H. tenuifolium* oleoresins are effective agents for patch test diagnosis of allergic contact dermatitis caused by the specific oleoresin, provided a potent product is employed.

The Panel has found only circumstantial evidence indicating the *H. microcephalum* and *H. tenuifolium* oleoresins are effective for immunotherapy, but recommends that on the basis of their analogy to proven, effective poison ivy and poison oak oleoresins, they should be available for immunotherapy.

The Panel recommends that the *Helenium* oleoresin products be placed in Category IIIA for patch test diagnosis and oral prophylactic immunotherapy.

Other Plant Oleoresins

The Panel recognizes that there is evidence indicating that other plant oleoresins may be effective for skin test diagnosis of allergic contact dermatitis (Refs. 1, 2, and 48). This is an area which should be explored further by experts in contact dermatitis. This is a potentially very large area and one that should be served by those doing active work in the field.

The Panel recommends that the other licensed plant oleoresin biologicals be placed in Category IIIA for patch test diagnosis and either Category IIIA or IIIB for oral immunotherapy comparable to the generic recommendations listed in Table 1.

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(83) BER Volumes 4011, 4025, 4025A, 4027, 4035, 4036, 4038, 4041 and 4042.

VII. Histamine Azoprotein (Hapamine®) (Lertigon®)

A. *Introduction.* Hapamine is a solution of histamine azoprotein recommended for use in treating certain allergic conditions.

It was licensed in 1943 to Parke, Davis and Co. The rationale for this product's use was based on the theory that the common causative mediator of allergic reactions is histamine released from tissue cells by an antigen-antibody reaction. Therefore, neutralization of histamine should relieve or reduce symptoms in allergic individuals exposed to the specific allergen or when physical situations cause a similar release of histamine.

Histamine by itself is not immunogenic, but antibodies can be produced against a histamine-protein complex, i.e., histamine can be a hapten (Refs. 1 ans 2). Fell et al. (Ref. 1) described the preparation of *p*-aminobezoyl histamine and its coupling through an azo linkage to despeciated (i.e., takadiastase treated) normal horse serum globulin and to other proteins. The hapten-protein complex contained no free histamine, but histamine could be liberated by hydrolysis with hydrochloric acid. Hyperimmunization of rabbits with the histamine azo-despeciated horse serum globulins (by the intravenous route) resulted in antiserum with a low precipitin titer (i.e., the hapten was a weak immunogen). Some of the antibodies appeared to be directed against the despeciated horse serum globulin. Specificity of the rabbit antiserum for histamine was suggested by inhibition of the precipitin reaction with histamine. Aminobenzoyl histamine and, to a lesser extent, histidine, also inhibited this reaction, though both were less effective than histamine. Reduction of the signs of anaphylaxis was observed in guinea pigs that had been given multiple injections of histamine azoprotein, then sensitized and challenged with ovalbumin. Other evidence that guinea pigs immunized with histamine azoprotein were more resistant to anaphylaxis than control animals included: (1) Lower levels of histamine in heart blood and (2) smaller local skin reactions after challenge with antigen and histamine. The contraction of sensitized guinea pig ileum challenged in vitro with antigen or histamine was reduced in the presence of rabbit antihistamine azoprotein serum.

Coffin and Kabat (Ref. 3) studied the effectiveness of histamine azoprotein in protecting guinea pigs against passive anaphylactic shock. Histamine azoprotein was administered subcutaneously to the animals either as an alum precipitate or in complete Freund's adjuvant. Subsequently, the treated animals exhibited no protection against a lethal does of histamine injected intravenously. On the other hand, guinea pigs treated with histamine azoprotein and sensitized with rabbit anti-eggalbumin were protected against a fatal anaphylactic does of egg albumin. However, the same degree of protection was seen in guinea pigs that had been immunized with human serum instead of histamine azoprotein. It was also observed that one or two subcutaneous injections of histamine azoprotein could sensitize a guinea pig so that fatal anaphylaxis resulted after an intravenous infection of histamine azoprotein. It was not established whether any antibodies were formed to the haptenic histamine.

More recently, Davis and Meade have linked histamine to rabbit serum albumin (RSA) using a basic carbodiimide (Ref. 2). The molar ratio of histamine to RSA in the complex was not reported. Precipitating antibodies to histamine-RSA were produced in guinea pigs by giving multiple injections of the complex in complete Freund's adjuvant. Serum from these guinea pigs was able to neutralize to a significant degree the biological effects of an LD_{50} does of histamine injected intravenously into normal guinea pigs; normal guinea pig serum did not neutralize histamine. No adverse effects on growth rate, overt behavior or physical appearance were observed in the actively immunized animals. The immunogenicity of histamine azoprotein (Hapamine) relative to histamine-RSA was not tested.

B. *Manufacturing.* Preparation of histamine azoprotein: Histamine is combined with p-nitrobenzoylchloride in chloroform and triethylamine. The resulting p-nitrobenzoyl histamine is reduced with ferrous sulfate and ammonia to give p-aminobenzoyl histamine; the latter is then obtained in crystalline form. This compound is diazotized with nitrous acid and mixed with the despeciated horse globulin in the cold. The azoprotein complex is salted out and then dialyzed first against tap water, then against 0.5 percent phenol. The product is diluted to contain 5 to 7 mg nitrogen/mL.

C. *Labeling.* The package insert (Ref. 4) notes that this product has been shown to stimulate a degree of immunity against histamine. The labeling says that the product "has been used to advantage in the treatment of the following allergic states" and then lists: "atopic asthma; vasomotor (allergic) rhinitis; physical allergy (heat, light, cold); contact dermatitis; atopic eczema; urticaria; seasonal hay fever (especially spring type); gastrointestinal allergy; vertigo; periodic headaches; liver extract sensitivity; and infantile eczema." It also mentions two reports that fail to confirm the observations of other investigators.

The labeling recommends that the product be administered subcutaneously, employing several dosage shedules increasing to maintenance levels as tolerance permits. It suggests that persons sensitive to horses or to horse serum should be tested for sensitivity to histamine azoprotein before treatment is started. Furthermore, it suggests that patients who have previoulsly received the product and with whom treatment is resumed after a lapse of time should be tested for sensitivity.

Labeling was also available for the product as sold in Canada, India, Australia, and other English- speaking countries, for Spanish speaking countries, and for bulk export to Mexico and Argentina.

D. *Safety*—1. *Animal studies.* The data submitted to the Panel (Ref. 4) contain the following information. Antigen-H (histamine azoprotein) was well tolerated by guinea pigs in doses of 0.75 to 1.5 mL per animal (route unspecified) twice weekly for 4 weeks. The LD_{50} intraperitoneally or subcutaneously in mice was 50 to 62.5 body weight. In rats, it exceeded 20 mL/kg. After daily intraperitoneal injection of 5 mL/kg body weight, mice showed increasing signs of toxicity in the second week; prolonged use made them more sensitive to the next dose. Rabbits were given 0.5 to 1.0 mL intravenously four times a week with no adverse effects. Horses tolerated 1 to 10 mL intracutaneously at several days' intervals for 1 month.

As noted above, Coffin and Kabat (Ref. 3) induced active sensitization in guinea pigs with one or two subcutaneous injections of alum-precipitated histamine azoprotein sufficient to produce fatal anaphylaxis when the animals were challenged intravenously 21 days later with histamine azoprotein.

2. *Human studies.* In the company data submission (Ref. 4) it was stated that 1 mL of histamine azoprotein given subcutaneously at weekly intervals to human subjects had produced no important local or systemic reactions. In

most subjects, mild inflammation occurred at the site of injection; it disappeared in 3 to 7 days. The material had been given to horse serum-sensitive individuals without reaction.

McLaurin (Ref. 5) mentioned 24 reactions in 18 of 102 patients being treated with histamine azoprotein either for vertigo, allergic rhinits, or dermatitis. Most reactions were local, at the site of the injection, and sometimes at the sites of all previous injections as well. Nine reactions took the form of asthmatic attacks; a few of these occurred in patients not previously subject to asthma. In four instances, there was transient aggravation of vertigo.

Dundy et al. (Ref. 6) reported 4 reactions among 40 cases (20 children and 20 adults) treated with histamine azoprotein by subcutaneous injection. In 1 child, vomiting occurred regularly within 2 hours of injection; in the other, recurrent marked local reactions occurred. In one adult, marked swelling of the arm and forearm and temperature elevation occurred; in the other, recurrent large local reactions occurred. All these reactions necessitated discontinuance of treatment.

Schwartz and Legere (Ref. 7) treated 11 patients among a group of 84 who were sensitive to liver extract with repeated subcutaneous doses of histamine azoprotein. No untoward results were noted with the exception of an occasional small tender mass which persisted for some days at the site of injection.

Smater (Ref. 8) administered increasing doses of from 0.1 to 0.5 mL of a 1:100 dilution of histamine azoprotein intravenously to 4 normal individuals at weekly intervals. Two days after the fifth injection, all the subjects gave positive immediate skin reactions to an intradermal injection of the dilution of histamine azoprotein used for treatment, and one subject developed a generalized urticaria after the next or sixth injection. Thus, even a short course of injections appears capable of inducing allergic sensitivity.

The manufacturer cited four reactions reported to it in the 5 years prior to the data submission (Ref. 4, p. 22). In the first instance, a patient was given 0.2 mL of the product into the frontal sinus and within 30 minutes developed pain in the lower extremities and clonic convulsions; diarrhea lasted for 3 days. The second report cited no details of the reaction. The thrid report mentioned a patient who developed swelling of the eyelids and dyspnea about 1 hour after receiving an injection of the product; this reaction responded promptly to adrenalin. The fourth report described a reaction similar to the third.

In 1943, a Parke, Davis and Co. scientist described the results of treatment of 289 patients with histamine azoprotein (Ref. 4, p. 23 to 23c). He stated that when the product was given intradermally there was usually a slight local skin reaction which might persist for a few days or a week and be succeeded by a small, pigmented macule. Subcutaneous injections occasionally caused a mild to moderately severe circumscribed area of infiltration; the associated edema and tenderness usually subsided within 12 to 48 hours. Systemic reactions were encountered in 2 to 3 percent of patients and might follow the first or any subsequent injection He stated that neither the amount nor the interval seemed to have any direct bearing on the occurrence of this general reaction. Several investigators had reported that allergic conditions frequently showed a sudden flare or exacerbation if the dose schedule of the product was increased too rapidly.

As noted previously, the package insert recommends that persons who are sensitive to horses or horse serum should be tested for sensitivity to histamine azoprotein (since it is derived from horse serum) before starting therapy with the product; no specific reference is cited to support this recommendation. There is no evidence regarding the long-term safety of this product.

E. *Standard of potency.* There is no recognized standard of potency. The product contained no detectable free histamine. After hydrolysis with hydrochloric acid, 0.25 to 1.05 mg (0.002 to 0.01 mMole) histamine (as free base)/mL is liberated. The total nitrogen content of the product is 5 to 7 mg/mL. The ratio of bound histamine to nitrogen ranged from 0.05 to 0.15 mg histamine/mg nitrogen.

F. *Effectiveness in therapy.* No controlled clinical trials have been conducted with this product. The product was licensed in 1943, a time when controlled clinical trials were not common.

Sheldon et al. (Ref. 9) were the first to describe the therapeutic use of histamine azoprotein. Seventy-six patients with a variety of conditions received the product for periods of up to 20 months. Responses varied considerably. There was no correlation between the dose of the product and the therapeutic results. Six patients with seasonal hay fever showed no improvement. Patients with physical allergies and with contact dermatitis, atopic eczema, or urticaria were said to respond most favorably.

McLaurin (Ref. 5) claimed generally good-to-excellent results in treating 40 cases of vertigo, 9 cases of periodic headaches, and 41 cases of vasomotor rhinitis.

Eder (Ref. 10) reported that he had used the product successfully in treating 17 children with allergic rhinitis; in 3 of them, their atopic dermatitis had also responded.

Johnson (Ref. 11) reported that 17 of 18 infants with infantile eczema were aided by treatment with histamine azoprotein.

The product was reported to be of value in the treatment of sensitivity to liver extract in 10 of 11 patients in whom it was used (Ref. 7). However, the authors suggested that this result "be interpreted with caution since spontaneous loss of sensitivity is so common."

Dundy et al. (Ref. 6) reported that among 40 patients with allergic disorders (9 with atopic eczema; 12 with asthma; 12 with rhinitis; 1 with papular urticaria; 4 with migraine; and 2 with angioneurotic edema), slight improvement was noted in 11. Not one of the patients showed a completely satisfactory result. The possibility of spontaneous remission or placebo effect was suggested to account for the improvement.

Cohen and Friedman (Ref. 12) reported the following results of treatment with histamine azoporotein in 55 patients: In 15 cases of urticaria, the results were excellent in 8, good in 3, and negative in 4. In 19 cases of asthma, results were excellent in 8, good in 1, and negative in 10. In five cases of contact eczema, results were excellent in two and negative in three. In seven cases of atopic eczema, results were excellent in one, good in three and negative in three. In three cases of vasomotor rhinitis, results were negative in all three. In six cases of hay fever, results were good in one and negative in five. The authors concluded that treatment with histamine azoprotein was of distinct value in urticaria and certain cases of asthma, while it was of no value when used alone in the prevention of hay fever. They further stated that, because histamine azoprotein is a poor antigen, it required about 4 months of treatment to obtain an adequate therapeutic response. It should be noted that these authors employed much larger doses than was recommended by the manufacturer; they began with 0.1 mL, and by the third dose gave 1.0 mL. After giving a total of 5 mL in the first series of injections, a rest period of 2 or 3 months was alllowed, after which a second series of injections

was given until a cumulative dose of 2.5 mL was reached.

Hebald et al. (Ref. 13) reported no clinical benefit in 13 patients with ragweed hay fever treated with histamine azoprotein.

Cohen and Friedman (Ref. 14) administered histamine azoprotein (up to 1.5 mL per injection) for a period of from 3 months to 1 year to a group of patients with various conditions. Serum from 5 out of 6 patients gave a positive reaction for antibody against histamine azoprotein in a collodion particle agglutination test; the maximum titer was 1:1280. Kabat and Mayer (Ref. 15) regarded this technique as erratic. A positive reaction was also observed when histamine azocasein was substituted for histamine azo-horse globulin, suggesting that the agglutinating activity of the serum was specific for either the histamine complex or the azo linkage of the histamine azo-horse globulin. To test whether the serum activity was directed against histamine, 1:1,000 histamine was added to the serum, and the collodion agglutination test was repeated. This resulted in inhibition of agglutination at all dilutions of serum tested (from 1:4 to 1:128). These authors also showed that histamine concentrations from 2- to 10-fold higher were required to induce a threshold skin wheal by iontophoresis in 3 out of 4 normal human subjects after the histamine was incubated for a period of from 10 to 50 minutes with a constant (but unspecified) amount of antihistamine azoprotein serum than when the histamine was diluted in saline. Why there was no difference in one of the test subjects was not explained; the same serum-histamine mixture was used in all cases. Controls in which the histamine was diluted in normal serum were not done. Serum from one subject appeared to inactivate approximately 25 percent of the added histamine (1:200,000) when the mixture of the serum and histamine was incubated at 37 °C for 24 hours before being assayed on guinea pig ileum. In discussion of this report, Dr. O. Swineford, Jr., said he regarded the controls as inadequate and suggested the work be repeated.

Sheldon et al. (Ref. 9) reported an experiment in which they incubated 0.1 mg of histamine phosphate with serum from each of 7 patients who had been treated with histamine azoprotein. After 24 hours incubation, each mixture was injected into the skin of 3 nonallergic people. Typical histamine wheals were produced by all the mixtures, suggesting that none of the sera neutralized the histamine.

Cohen and Friedman (Ref. 16) reported that the skin threshold to histamine was higher than normal in 8 of 10 patients who had been treated for varying periods of time with relatively large doses of histamine azoprotein. The patients' threshold to histamine was not tested prior to the initiation of therapy, and the report lacks other information which is necessary to substantiate the authors' conclusion.

Hebald et al. (Ref. 13) treated ragweed hay fever patients with histamine azoprotein, with cumulative dosages ranging from 2.3 mL to 20 mL. In six patients, the skin threshold response to histamine was not altered by the therapy. In serum from five patients, precipitating antibodies to histamine azoprotein were demonstrable after therapy, but these antibodies were not precipitated by histamine azocasein, indicating that the antibodies were not specific for the haptenic histamine.

G. *Critique.* Most of the literature dealing with this product is more than 30 years old. The weight of evidence presented by these studies favors the views of Kabat (Ref. 3) and Cooke (Ref. 13), who were unable to demonstrate the existence of histamine-specific antibodies in animals and human subjects following multiple injections of histamine azoprotein. None of the favorable clinical results that have been reported were obtained in controlled clinical trials; most of the evidence was derived from anecdotal case reports. Furthermore, the best results were often obtained in those conditions (e.g., contact dermatitis, vertigo, periodic headaches) in which it seems that histamine is least likely to be implicated as a mediator. The fact that patients with conditions which are presumably not mediated by histamine seem to be helped most suggests that the produce is acting either as a placebo or nonspecifically, as suggested by Coffin and Kabat (Ref. 3).

The Panel concluded that, after 30 years, the scientific basis of this treatment would have been indisputably established were there truly a histamine-neutralizing effect resulting from immunization with histamine azoprotein. This evidence has not been produced. Furthermore, there appears to be a significant rate of adverse reactions including local and systemic anaphylaxis (which could be due to coexistent allergy to horses or to horse serum proteins, or more likely is due to the development of anaphylactic antibodies against the protein component of the product), so that therapy with this product is not without risk.

H. *Recommendation.* Since the therapeutic effectiveness of this product has not been established and, in fact, remains in serious doubt, and since there is a significant risk of inducing sensitivity during a course of therapy with this product, the Panel recommended that this product, histamine azoprotein (Hapamine), be placed in Category II. After the review of this product by the Panel, the manufacturer voluntarily withdrew the product license on February 9, 1978.

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VIII. FDA's Response to the Panel's Recommendations

Most of the extracts reviewed by the Panel were classified into categories on a generic basis. In addition, most extracts are approved under a "blanket license" for allergenic extract manufacturers. While a small number of manufacturers produce only a few extracts, or even one extract, other manufacturers produce several hundred extracts under the approved license application. Therefore, for the product discussions that follow and the listing under item A.4. below, the manufacturer will be listed with the product only in those cases where the product is approved under a specific product license, or the specific manufacturer's product was reviewed by the Panel. For the convenience of the reader, all the licensed manufacturers of products reviewed by the Panel are listed as follows:

Allergy Laboratories of Ohio, Inc., License No. 407;

Allergy Laboratories, Inc., License No. 103;

Allermed Laboratories, Inc., License No. 467;

Antigen Laboratories, Inc., License No. 468;

Barry Laboratories, Inc., License No. 119;

Berkeley Biologicals, License No. 334;

Cutter* Laboratories Inc., License No. 008;

EM Industries, Inc., Center Laboratories Division, License No. 193;

Endo Laboratories Inc., License No. 147 (This license was revoked at the request of the manufacturer on August 20, 1981);

Greer Laboratories, License No. 308;

Iatric Corporation, License No. 416;

Merck Sharp and Dohme, Division of Merck and Co., License No. 002;

Meridian Bio-Medical, Inc., License No. 448;

Miles* Laboratories, Inc., License No. 362;

Mulford Colloid Laboratories Division of Lemmon Co., License No. 102;

Nelco Laboratories, Inc., License No. 459;

Parke-Davis, Division of Warner Lambert Co., License No. 001;

Pharmacia AB, License No. 752;

Pharmacia Laboratories Division of Pharmacia, Inc., License No. 556 (This license was revoked at the request of the manufacturer on February 24, 1982);

Riker Laboratories, Inc., License No. 372; and

Washington Homeopathic Pharmacy, Inc., License No. 392;

FDA is responding to the Panel's recommendations as follows:

A Product Classifications

The Panel recommended that allergenic extracts be grouped into regulatory categories as follows:

1. *Category I. Biological products determined to be safe and effective and not misbranded and which may continue in interstate commerce:* The Panel recommended that several products be placed in Category I on a generic basis, but found that the basis submissions for specific products were insufficient to recommend that any specific products be classified in Category I. Therefore, if the Panel recommended that the extract be placed in Category I on a generic basis, each respective extract of each licensed manufacturer was recommended to be placed in Category IIIA. The Panel believed that many of the specific products would be found to be effective, if appropriate studies were conducted. In addition, the Panel noted that for the newer hymenoptera venoms or short ragweed pollen extracts with potency standards, there are clinical data demonstrating safety and effectiveness, and the potency of these products can be correlated with the biological activity of the allergens (e.g., venom enzymes and antigen E) used in the development of the clinical data. The Panel recommended that when data of this type are developed for a product, the product should be approved by FDA for Category I. Indeed, during the Panel's review, Hollister-Stier Labs., Division of Cutter Labs., Inc., submitted an amendment to its license application which included data on antigen E standardization of short ragweed pollen extracts. The amendment was approved, and FDA considers that specific product to have met the Category I criteria at the time the amendment was approved.

FDA agrees with the Panel's findings and recommendations concerning the generic Category I classifications and hereby proposes to adopt its conclusions, including all labeling and other license amendment recommendations of the Panel concerning product use that are accepted by FDA, and which must be made a part of each manufacturer's license application. Therefore, FDA proposes that only two generic products applicable to all manufacturers be in Category I: Standardized hymenoptera insect venons and short ragweed pollen extracts with approved antigen E labeling. Since the Panel completed its review, various manufacturers have obtained approval for amended license applications to standardize certain specific extracts by methods such as RAST or quantitation of Cat Allergen I. FDA considers those specific products for which license amendments have approved to have met the criteria for classification as a Category I product.

FDA invites the submission of comments and additional data on these proposed classifications. FDA notes that the proposed Category I classification for hymenoptera venoms does not include Honeybee Venom for diagnostic use by Center Labs., Inc., which FDA proposes be in Category IIIA.

2. *Category II. Biological products determined to be unsafe or ineffective or to be misbranded and which should not continue in interstate commerce:* Histamine Azoprotein, Parke-Davis, Division of Warner-Lambert Co. and Aspergillus extracts for use in immunotherapy of bronchopulmonary aspergillosis.

FDA agrees with the Panel's findings and recommendations concerning these products. The agency notes that the authority of Parke-Davis to produce Histamine Azoprotein was revoked at the firm's request on February 9, 1978. Also, FDA notes that Aspergillus extracts were recommended generically for Category I for diagnosis and Category IIIA for immunotherapy of asthma and rhinitis. FDA has not previously approved any Aspergillus extracts for immunotherapy of bronochopulmonary aspergillosis, nor is the agency aware of the extracts being used for such immunotherapy. Accordingly, FDA proposes no actions for the Category II products.

3. *Category IIIA. Biological products for which available data are insufficient to classify their safety and effectiveness but which may remain in interstate commerce pending completion of testing:* The Panel recommended that most allergenic extracts be placed in Category IIIA. The classification would affect nearly 6,500 specific company products. However, since the Panel completed its review, the agency has issued a new rule that eliminates

*Since the Panel completed its review, Cutter Laboratories, including its Hollister-Stier Labs., has become a part of Miles Laboratories, Inc., and the combined operations are now licensed under License No. 008. In the following discussions and listings under *Product Classifications* the references to specific products manufactured by Hollister-Stier Labs., Division of Cutter Labs., Inc., or by Miles Laboratories, Inc., apply to the products manufactured by those companies at the time the Panel completed its review and before the merger of the two companies. Any notice of opportunity for hearing resulting from this proposal concerning any products manufactured by either of the two companies during the Panel's review will apply to the present company (Miles Laboratories, Inc.) licensed under U.S. License 008.

Category IIIA and provides for the reclassification of all Category IIIA biological products, including allergenic extracts, by new advisory committees. All Category IIIA products will be reclassified into either Category I or Category II. These rules were published in the **Federal Register** of October 5, 1982 (47 FR 44062). Therefore, all allergenic extracts recommended for Category IIIA will be reviewed by the appropriate advisory committee. FDA will publish a separate proposal concerning these products following its review of the advisory committee's recommendations. Because the Category IIIA classification has been eliminated, the products recommended for that category by the Panel on Review of Allergenic Extracts will not be listed in the agency's response to the Panel's report.

4. *Category IIIB. Biological products for which available safety and effectiveness data are insufficient to classify them into Category I or II and which should not continue in interstate commerce:* The products recommended for Category IIIB are listed in the following table. Some products were recommended for Category IIIB for immunotherapy and a different cateogry for diagnosis. In addition, some products are approved only for immunotheraphy. Therefore, the following table lists a product under "diagnosis" or "therapy" only if the Panel recommended and FDA proposes that it be placed in Category IIIB for that particular use. For convenience, the products are listed here as listed in the Panel's report.

EXTRACTS OF MAMMALIAN ORIGIN—PROPOSED FOR CATEGORY IIIB

Diagnosis	Immunotheraphy
Angora wool, rabbit and antelope hair mix.	Angora wool, rabbit and antelope hair mix.
Beaver fur	Beaver fur.
Caracul fur	Caracul fur.
Chamois skin	Chamois skin.
Chinchilla fur	Chinchilla fur.
Ermine fur	Ermine fur.
Fox fur	Fox fur.
Fur mix	Fur mix.
Gerbil fur	Gerbil fur.
Kolinsky fur	Kolinsky fur.
Lamb, black	Lamb, black.
Leopard fur	Leopard fur.
Marmot fur	Marmot fur.
Mink fur	Mink fur.
Mole fur	Mole fur.
Muskrat fur	Muskrat fur.
Muskrat fur (Hudson seal)	Muskrat fur (Hudson seal).
Nutria fur	Nutria fur.
Opossum fur	Opossum fur.
Persian lamb fur	Persian lamb fur.
Pony fur	Pony fur.
Rabbit hair (fur)	Rabbit hair (fur).
Raccoon fur	Raccoon fur.
Sable fur	Sable fur.
Seal fur, Alaskan	Seal fur, Alaskan.
Seal fur	Seal fur.
Sheep wool	Sheep wool.
Skunk fur	Skunk fur.
Squirrel fur	Squirrel fur.

FOOD EXTRACTS—PROPOSED FOR CAGETORY IIIB

Diagnosis	Therapy
Anchovy/Herring/Sardine	Anchovy/Herring/Sardine.
Angostura Bitters	Angostura Bitters.
Apple Mix	Apple Mix.
Bacon	Bacon.
Bean Sprouts	Bean Sprouts.
	Beechnut: *Fagus sylvatica.*
Beer	Beer.
Buttermilk	Buttermilk.
Cascara Bark: Rhamnus purshiana.	Cascara Bark: Rhamnus purshiana.
Caviar	Caviar.
Cheese, Americn	Cheese, American.
Cheese, Camembert	Cheese, Camembert.
Cheese, Cheddar (American)	Cheese, Cheddar (American).
Cheese, Cottage	Cheese, Cottage.
Limburger	Cheese Limburger.
Cheese, Mazzarella	Cheese, Mazzarella.
Cheese, Parmesan	Chees, Parmesan.
Cheese, Pimento	Cheese, Pimento.
Cheese, Provolone	Cheese, Provolone.
Cheese, Romano	Cheese, Romano.
Cheese, Roquefort	Cheese, Roquefort.
Cheese, Swiss	Cheese, Swiss.
Cherry, Mix	Cherry, Mix.
Chewing Gum Base	Chewing Gum Base.
Chili Power	Chili Powder.
Chocolate	Chocolate.
Cider, Apple	Cider, Apple.
Cocoa	Cocoa.
Cocoa (Hersheys)	Cocoa (Hersheys).
Coco-Cola	Coco-Cola.
Cola	Cola.
Cola-Glyoune	Cola-Glyoune.
	Coffee: *Coffea arabica.*
Cream of Tartar	Cream of Tartar.
Curry Powder	Curry Powder.
Dr. Pepper	Dr. Pepper.
Gelatin	Gelatin.
Grape/Raisin Mix	Grape/Raisin Mix.
Grape, Raisin	Grape, Raisin.
Ham Smoked	Ham Smoked.
Honey	Honey.
Honey, Pure	Honey, Pure.
Lactalbumin	Lactalbumin.
Lactalbumin, Cow's Milk	Lactabumin Cow's Milk.
Lettuce Mix: *Lactuca sativa species.*	Lettuce Mix *Lactuca sativa species.*
	Licorice: *Glycyrrhiza glabra.*
Liver	Liver.
Milk, Condensed	Milk Condensed.
Milk (evaporated)	Milk (evaporated).
Mint Mix: Peppermint-*Mentha piperita* and Spearmint-*Mentha spicata.*	Mint Mix; Peppermint-*Mentha piperita* and Spearmint-*Mentha spicata.*
Mull-Soy	Mull-Soy.
Mollasses	Mollasses.
Muskmelon Mix (Cantaloupe/Casaba/Honeydew/Persian): *Cucumis melo.*	Muskmelon Mix (Cantaloupe/Casaba/Honeydew/Persian): *Cucumis melo.*
Mustard, Prepared	Mustard, Prepared.
Oatmeal	Oatmeal.
Olive Mix	Olive Mix.
Onion Mix	Onion Mix.
Pablum	Pablum.
Mixed Peppers (Red and Green).	Mixed Peppers (Red and Green).
Pepsi-Cola	Pepsi-Cola.
Plum/Prune Mix	Plum/Prune Mix.
Popcorn Seed: *Zea Mays*	Popcorn Seed: *Zea Mays.*
Postum	Postum.
Prune, Dried	Prune, Dried.
Raisin	Raisin.
Root Beer	Root Beer.
Saccharose	Saccharose.
Saccharin	Saccharin.
Seven-up	Seven-up.
Squahs: *Cucurbita pepo* varieties.	Squash: *Cucurbita pepo* varieties.
Squash Mix	Squash Mix.
Sugar (Beet): *Beta vulgaris.*	Sugar (Sugar (Beet: *Beta vulgaris.*
Sugar (Cane): *Saccharum officinarum.*	Sugar (Cane): *Saccharum officinarum.*
Sugar (Maple): *Acer saccharum.*	Sugar (Maple) *Acer saccharum.*
Sweetbreads	Sweetbreads.
Syrup, Pure Maple	Syrup, Pure Maple.
Tea, Black	Tea, Black.
Tea, Green	Tea Green.

FOOD EXTRACTS—PROPOSED FOR CAGETORY IIIB—Continued

Diagnosis	Therapy
Tea, Mixed	Tea, Mixed.
Tuna Mix	Tuna Mix.
Vinegar	Vinegar.
Worcestershire Sauce	Worcestershire Sauce.
Yeast: *Saccharomycetaceae*	Yeast: *Saccharomycetaceae.*
Yeast Mix (Bakers/Brewers)	Yeast Mix (Bakers/Brewers).

MISCELLANEOUS INHALANT EXTRACTS—PROPOSED FOR CATEGORY IIIB

Diagnosis	Therapy
Animal Feed Mix	Animal Feed Mix.
Balsam Sawdust	Balsam Sawdust.
Binder Twine	Binder Twine.
Cattail	Cattail.
Chalk	Chalk.
Cleaning Tissue	Cleansing Tissue.
	Cottonseed.
Dacron	Dacron.
	Derris Root.
Dust, Alfalfa Hay	Dust, Alfalfa Hay.
Dust, Alfalfa Mill	Dust, Alfalfa Mill.
Dust, Auto Upholstery	Dust, Auto Upholstery.
Dust, Barley	Dust Barley.
Dust, Barn	Dust, Barn.
Dust, Brome Corn	Dust, Brome Corn.
Dust, Chicken House	Dust, Chicken House.
Dust, Clover Hay	Dust, Clover Hay.
Dust, Combined	Dust, Combined.
Dust, Furniture Upholstery	Dust, Furniture Upholstery.
Dust, Hay	Dust, Hay.
Dust, Prarie Hay	Dust, Prarie Hay.
Dust, Kafir	Dust, Kafir.
Dust, Lespedeza Hay	Dust, Lespedeza Hay.
Dust, Milo	Dust, Milo.
Dust, Oat	Dust, Oat.
Dust, Pea	Dust, Pea.
Dust, Pencil	Dust, Pencil.
Dust, Poultry	Dust, Poultry.
Dust, Rice	Dust, Rice.
Dust, Road	Dust, Road.
Dust, Rye	Dust, Rye.
Dust, Soy Bean	Dust, Soy Bean.
Dust, Timothy Hay	Dust, Timothy Hay.
Dust, Wheat	Dust, Wheat.
Excelsior	Excelsior.
Fiber Glass	Fiber Glass.
	Flaxseed.
Glue	Glue.
Glue, Animal	Glue, Animal.
Glue, Fish	Glue, Fish.
Glue, Liquid	Glue, Liquid.
Glue, Powdered	Glue, Powdered.
Lampblack	Lampblack.
Linen	Linen.
Newspaper	Newspaper.
Newspaper Mix (Printed)	Newspaper Mix (Printed).
Newspaper/Newspaper Print	Newspaper/Newspaper Print.
Nylon	Nylon.
Paper, Mix	Paper, Mix.
Paper, Carbon	Paper, Carbon.
Paper, Pulp	Paper, Pulp.
Rayon	Rayon.
Rug	Rug.
Smoke, Cigar	Smoke, Cigar.
Smoke, Cigarette	Smoke, Cigarette.
Smoke, Tobacco	Smoke, Tobacco.
Tobacco Smoke Mixture	Tobacco Smoke Mixture.
Snuff, Mix	Snuff, Mix.
Spanish Moss	Spanish Moss.
Tobacco, Cigar	Tobacco, Cigar.
Tobacco, Cigarette	Tobacco, Cigarette.
Tobacco, Mix	Tobacco, Mix.
Tobacco, Pipe	Tobacco, Pipe.

PLANT OLEORESINS—PROPOSED FOR CATEGORY IIIB

Diagnosis	Therapy
	Injectable Plant Oleoresins.

PLANT OLEORESINS—PROPOSED FOR CATEGORY IIIB—Continued

Diagnosis	Therapy
	Poison Ivy Extracts, injection in almond oil, manufactured by Parke-Davis and Co.
	Poison Ivy Extract, injection in olive oil, (Ivyol ™), manufactured by Merck Sharp and Dohme, Division of Merck and Co. At the request of the manufacturer, this product license was revoked on December 6, 1978.
	Poison Ivy Extract, Poison Oak Extract and Poison Ivy-Poison Oak Extracts (combined), injections in alcohol, manufactured by Hollister-Stier Labs., Division of Cutter Labs., Inc.
	Poison Ivy Extract, injection in hydro-alcoholic solution (Rhustox Antigen ™), manufactured by Mulford Colloid Labs., Division of Lemmon Co.
	Poison Ivy-Oak-Sumac Extracts, combined, injection in almond oil, (Rhus-All Antigen ™), manufactured by Barry Labs., Inc.
	Poison Ivy Extract, Alum Precipitated, (Aqua Ivy ap ™), injection, manufactured by Miles Labs., Inc.
	Plant Oleoresin (for oral use only):
	Poison Ivy Extract by Washington Homeopathic Parmacy.
	The Panel suggested that FDA may wish to consider this product differently because it is a homeopathic remedy. However, FDA proposes that this biological product should be subject to the same regulatory procedures as other Category IIIB biologicals.
	Plant Oleoresins Used for Patch Testing and Oral Immunotherapy: Wild Plants, as follows:
	Aster *Callistephus.*
	Bitterweed *Helenium tenuifolium.*
	Black-eyed Susan *Rudbeckia hirta.*
	Burdock *Arctium.*
	Burweed marshelder *Iva xanthifolia.*
	Chicory *Chichorium Intybus L.*
	Cocklebur *Xanthium commune.*
	Dandelion *Taraxacum officinale.*
	Dog Fennel *Athemis cotula.*
	Fleabane *Erigeron.*
	Goldenrod *Solidago.*
	Ironweed *Veronia.*
	Ragweed, false *Franseria acanthicarpa.*
	Ragweed, giant *Ambrosia trifida.*
	Ragweed, western *A. psilostachya.*
	Sagebrush *Artemesia tridentata.*
	Sneezeweed *Helenium microcephalum.*
	Wild feverfew *Parthemium hysteroporus.*
	Wormwood *Artemesia absinthium.*
	Yarrow *Achillae lanulosa.*

PLANT OLEORESINS—PROPOSED FOR CATEGORY IIIB—Continued

Diagnosis	Therapy
	Chrysanthemum *Chrysanthemum x-morifolium.*
	Coreopsis *Coreopsis.*
	Corn flower.
	Cosmos *cosmos.*
	Dahlia *dahlia.*
	Feverfew *Chrysanthemum parthenium.*
	Gaillardia *gaillardia.*
	Lettuce *Latuca sativa* L.
	Marigold *tagetus.*
	Shasta daisy *Chrysanthemum maximum.*
	Sunflower *Helianthease.*
	Tansy *Tanacetum vulgare* L.

EXTRACTS OF MOLDS INVOLVED IN DERMATOMYCOSIS—PROPOSED FOR CATEGORY IIIB

Diagnosis	Therapy
Dermatophytin—Hollister-Stier Labs., Division of Cutter Labs., Inc.	Dermatophytin—Hollister-Stier Labs., Division of Cutter Labs., Inc.
Dermatophytin "O"—Hollister-Stier Labs., Division of Cutter Labs., Inc.	Dermatophytin "O"—Hollister-Stier Labs., Division of Cutter Labs., Inc.
"T.O.E."—Hollister-Stier Labs., Division of Cutter Labs., Inc.	"T.O.E."—Hollister-Stier Labs., Division of Cutter Labs., Inc.
"T.O.E."—Antigen Laboratories, Inc.	"T.O.E."—Antigen Laboratories, Inc.

EXTRACTS OF INSECTS—PROPOSED FOR CATEGORY IIIB

Diagnosis	Therapy
	Bedbugs.
Bee, Bumble	Bee, Bumble.
Bee, Honey; used for stinging insect anaphylaxis.	Bee, Honey; used for stinging insect anaphylaxis.
Bee, Sweat	Bee, Sweat.
	Beetle, Blister.
	Beetle, Dermestid.
	Beetle, Japanese.
	Beetle, Ladybug.
Black-fly	Black-fly.
Box Elder Bugs	Box Elder Bugs.
	Butterfly.
Caterpillar	Caterpillar.
Caterpillar (tent)	Caterpillar (tent).
Citrus Mealy bugs	Citrus Mealy bugs.
Clear Lake Gnats	Clear Lake Gnats.
	Cricket.
	Cicada/Locust.
	Cockroach.
	Cockroach, Mixed.
	Daphnia.
	Flea.
	Flea, Dog.
	Flea, Cat.
	Flea, Mixed.
Flea, Sand	Flea, Sand.
	Flea, Water (daphnia pulex).
	Fruit Flies.
Gant	Gant.
Gant, Black	Gant, Black.
Grasshopper	Grasshopper.
Hornet	Hornet.
Hornet, Bald Face	Hornet, Bald Face.
Hornet, Black and Yellow Mix	Hornet, Black and Yellow Mix.
Hornet, Japanese	Hornet, Japanese.
Horsefly	Horsefly.
Horsefly/Stable Fly	Horsefly/Stable Fly.
	Housefly.
Household Insects	Household Insects.
	Leafhopper.
	Locust.
	Mosquito.
	Mosquito Mix.
	Moth.
	Moth/Miller.

EXTRACTS OF INSECTS—PROPOSED FOR CATEGORY IIIB—Continued

Diagnosis	Therapy
Sandfly	Sandfly.
	Screwworm Fly.
	Sow Bugs.
	Spider.
	Spider Mix.
Stable Flies	Stable Flies.
Tick Seeds	Tick Seeds.
	Triatoma.
Wasp	Wasp.
Wasp Mix	Wasp Mix.
Yellow Jacket	Yellow Jacket.
Stinging Insect Mix	Stinging Insect Mix.

In addition, Allergenic Extracts, Alum-Precipitated (approved for therapy only) licensed to Center Labs., Inc., were recommended as Category IIIB when the corresponding aqueous product was placed in Category IIIB. Allergenic Extracts, Alum-Precipitated (Allpyral Extracts) licensed to Miles Laboratory were recommended for Category IIIB when the corresponding aqueous extracts were recommended for Category IIIB, and which includes wool extract and whole body winged hymenoptera extracts for insect sting allergy. Also, Allpyral short ragweed pollen extract was recommended for Category IIIB because the bulk of the applicable data and information available to the Panel suggested that this product is not effective.

FDA agrees with the Panel's findings and recommendations concerning the Category IIIB allergenic extracts discussed above and, in accordance with § 601.5 (21 CFR 601.5), intends to publish a Notice of Opportunity for Hearing on the proposal to revoke the approval under the license application or the product license, as applicable, for the manufacture of these products. Manufacturers would be required to amend their license applications to delete any product(s) recommended for Category IIIB for diagnos s and/or therapy that are manufactured and marketed under the approved license. For any product recommended generically for Category I or Category IIIA for diagnosis, but recommended for Category IIIB only for its use in immunotherapy, FDA is proposing that the label and the "Indications and Usage" section (21 CFR 201.57(c)) of the package insert indicate prominently, "FOR DIAGNOSTIC USE." The package insert (in the "Indications and Usage" section) should also include a statement that the rationale for therapeutic use of the product has not been established. The labeling requirement will become effective 180 days after the date of publication in the **Federal Register** of a

notice of opportunity for hearing on the Category IIIB products.

FDA notes that the Panel recommended that extracts of Cockroach, American; Cockroach, German; and Cockroach, Oriental be placed into category IIIB for immunotherapy. However, after the Panel completed its review, new relevant data were published that justify reconsideration of the generic classification of these products into Category IIIA. A copy of these published data has been placed on file with the Dockets Management Branch. Accordingly, Cockroach, American; Cockroach, German; Cockroach, Oriental; and mixtures consisting of such extracts will remain on the market on an interim basis pending review with all other Category IIIA products by the appropriate advisory committee for reclassification into either Category I or Category II.

In addition, the Panel recommended that extracts of Beechnut: *Fagus sylvatica*, Coffee: *Coffea arabica*, Licorice: *Glycyrrhiza glabra*, and Butterfly be placed into Category IIIB for both diagnosis and therapy. However, the data relating to these products were re-reviewed by the appropriate advisory committee, which has tentatively recommended reclassification of these products into Category I for diagnostic use. Therefore, FDA believes that these products should not be removed from the market at this time and will hold in abeyance and regulatory action, other than labeling changes, concerning the diagnostic use of these products. Accordingly, extracts of Beechnut: *Fagus sylvatica*, Coffee: *Coffea arabica*, Licorice: *Glycyrrhiza glabra*, and Butterfly will remain on the market for diagnostic use on an interim basis pending review by the agency of the final report of the appropriate advisory committee containing the recommendations for reclassification of the extracts into either Category I or Category II.

B. Safety

1. The Panel recommended that manufacturers use procedures for the control of mycotoxins in allergenic extracts. The Panel further recommended that FDA determine whether mycotoxins are detectable in a large selective sampling of extracts that potentially may be contaminated and identify those extracts for which assay of each final lot is to be required.

FDA agrees that manufacturers should use manufacturing and testing procedures that ensure control of mycotoxins, including aflatoxins, in allergenic extracts. FDA is proposing that manufacturers amend their standard operating procedures in the license applications, where appropriate, to specify the steps taken to control mycotoxin. FDA believes that the Panel's recommended mycotoxin control procedures concerning certain mold, house dust, pollen, epidermal, and food extracts are useful guides for manufacturers. FDA and certain manufacturers have performed some studies for the detection of certain mycotoxins in a sampling of products and information discussing the results of those studies has been placed on file with the Dockets Management Branch. Although FDA shares the Panel's concern that mycotoxins represent a potential health hazard in allergenic extracts used for skin test diagnosis and immunotherapy, the agency now believes that, based on the data available to date, a significant mycotoxin contamination problem does not exist. FDA believes that at this time manufacturers are following the mycotoxin control procedures in their license applications and, therefore, additional regulatory initiatives or lot release of final products based on assay for mycotoxins are unnecessary. FDA is, however, conducting a testing survey of selected allergenic extracts for detection of the presence of aflatoxins, and if the results of that survey show that a problem exists, FDA will take further action.

2. The Panel recommended that manufacturing steps for allergenic extracts be designed to limit bacterial contamination.

FDA agrees with this recommendation and notes that manufacturers are subject to all applicable good manufacturing practice regulations (21 CFR Parts 210 and 211) and biologics regulations intended to limit or eliminate bacterial contamination. In addition, the agency advises that extraction of the allergen shall be performed consistent with the conditions described in the manufacturer's license application, which should specify extraction conditions and require filtration of the extract as soon as possible after extraction. All equipment and utensils used in the manufacture, processing, packing, or holding of an allergenic extract shall be cleaned and maintained as requird under § 211.67 (21 CFR 211.67).

C. Labeling: General

1. The Panel recommended that the container label, package label, and package insert include certain information to be consistent with FDA regulations to ensure that the labeling contains the essential scientific information for the safe and effective use of the product.

FDA agrees with this recommendation, and notes that the existing regulations under §§ 610.60 and 610.61 (21 CFR 610.60 and 610.61) contain items that shall appear on the container label and package label, respectively. The content and format of the package insert labeling shall be consistent with the requirements specified under §§ 201.56 and 201.57 (21 CFR 201.56 and 201.57). All labeling changes proposed in this document must be submitted to the Director, Office of Biologics Research and Review, and may not become effective until notification of acceptance of the changes has been received from the Office of Biologics Research and Review (21 CFR 610.12). Under § 201.59(a)(3), the due date for submission to FDA of revised labeling required under §§ 201.56 and 201.57 is 6 months after a final rule has been published responsive to this proposal. The effective date for labeling changes submitted to and approved by the Director, Office of Biologics Research and Review, is 2 years after the due date or 30 months after publication of the final rule. (See 46 FR 7272.)

2. The Panel believes that manufacturers should not engage in any activities that might be construed as engaging in the practice of medicine. The areas of concern to the Panel are: (1) Formulation of diagnostic kits; (2) determination of the formula of individual patient therapeutic extract mixtures; and (3) preparation of specific dose schedules for therapeutic extracts. However, the Panel recommended that manufacturers should be permitted to use promotional labeling material and/or advertising to make supported statements on the quality, efficacy, safety, etc. of their products in order to encourage physicians to use them.

FDA agrees with this recommendation. The agency believes that manufacturers may use factual information in any promotional labeling or advertising that includes recommendations for use of the product as long as such labeling complies with FDA regulations, including 21 CFR Part 202. Manufacturers should not, however, imply in labeling that either the results of in-vitro assays of the patient's specific IgE or skin test results alone are satisfactory as the sole basis for the formulation and use of its extracts unless the manufacturer has conducted clinical studies that establish a correlation between the test results and such clinical studies. Further, FDA is proposing that manufactureres who are

engaged in the preparation of allergenic extract prescription mixtures for a specific patient specify in the product license application that they will obtain a signed prescription from the attending physician which designates the specific allergens (and concentration) that are required for preparing the mixture. This requirement will ensure that manufacturers do not determine the therapeutic extract mixture formula for individual patients. Of course, use of promotional labeling or advertising that is consistent with FDA regulations and is fairly balanced with information related to side effects, contraindications, and effectiveness is not prohibited and should not interfere with the physician's responsibilities for supervision of the diagnostic and therapeutic medical procedures suitable for a specific patient, including decisions affecting the selection of the appropriate extract concentration and treatment dose.

D. Source Materials

1. The Panel made several general recommendations concerning source materials for allergenic products. It recommended that source materials be:

a. Obtained from qualified collectors who use appropriate collection procedures;

b. Specifically identified and not contain avoidable foreign substances; and

c. Stored in a manner to minimize or arrest deterioration.

FDA concurs with the Panel's recommendations because the agency believes that allergenic extracts cannot be manufactured properly without authentic source materials that are in a condition appropriate for yielding their allergens. Currently, source materials must meet the requirements in § 680.1(b)(1) (21 CFR 680.1(b)(1)). A final rule was published in the **Federal Register** of June 21, 1984 (49 FR 25430) that amended § 680.1)(b) to establish specific criteria for molds and animals used as source materials for allergenic extracts. In the future, as technical knowledge permits, FDA will publish other proposals for source materials that will ensure the production of allergenic products that are safe, pure, potent, and efficacious.

2. The Penel recommended that FDA have inspection access to sources and collectors.

FDA notes that the agency now has the authority to inspect source materials and suppliers. See response to recommendation D1, above.

3. The Panel recommended that manufacturers maintain written standard operating procedures concerning source materials that are approved by FDA. These written standard operating procedures should define for each source material the estalished acceptance criteria, methods of identity testing, procedures for processing and storage, and labeling.

FDA agrees that the manufacturer should have such written standard operating procedures and notes that when source materials are prepared by a licensed manufacturer, the standard operating procedures should be part of the licensed manufacturer's product license application. In § 680.2(f) of the June 21, 1984 final rule, FDA required that nonlicensed manufacturers of allergenic source materials that are intended for use in manufacturing final licensed extracts maintain records of the history of the manufacture or propagation of each lot of source material.

4. The Panel made many specific recommendations for source materials for the following categories of allergenic extracts: (1) Epidermal; (2) food; (3) mold; (4) pollen; (5) house dust; and (6) miscellaneous inhalent.

FDA concurs with most of these specific recommendations. FDA will include the recommendations in specific proposals that it will develop in the future for the appropriate source material. In addition, FDA notes that the Panel recommended that contamination of a pollen species product with other pollen species should not exceed 1.0 percent with mixed pollens of other pollen species or 0.5 percent with a single pollen species, as determined by microscopic particle count. The Panel also recommended that the processed pollen contain no more than 10 percent contamination of nonpollen contaminants, e.g., plant debris, as determined by microscopic particle count. The regulation under § 680.1(b) now requires that a source material, including pollens, contain no more than 1.0 percent of detectable foreign materials.

FDA believes that manufacturers must take precautions necessary to ensure that a pollen of suitable purity and quality is used for the manufacture of an allergenic extract. However, the agency is aware that some pollens, such as those from certain plants that are insect pollinated, are more difficult to collect in a pure state than other pollens, such as pollens from certain plants that produce airborne pollens. Therefore, FDA believes that it would not be appropriate, at this time, to require that the contamination limits recommended by the Panel apply to all species of pollens. Rather, FDA is proposing herein that each manufacturer amend its license application to include as a standard operating procedure a method, approved by the Director, Office of Biologics Research and Review, for determining the contamination level in a batch of pollen intended for manufacture of an allergenic extract. The license amendment must specify the acceptable contamination limits for each species of pollen. FDA advises that the acceptable limit for mold spore contamination of pollens may not exceed 1.0 percent in order to minimize the concentration of the mold in the final extract. In addition, the agency is proposing that pollens determined to contain more than 1.0 percent contamination of foreign materials other than mold spores may be used for manufacture, only if the final product labeling identifies the assayed level of contamination in the batch of pollen used to produce the product.

Accordingly, FDA is proposing herein to amend § 680.1(b) by adding new § 680.1(b)(4) to require that (1) the amount of foreign materials in pollens be determined by a method approved by the Director, Office of Biologics Research and Review; (2) pollens determined to contain more than 1.0 percent of foreign materials (other than mold spores) may be used in the manufacture of allergenic extracts if the assayed amount of contamination is identified in the product labeling; and (3) pollens contain no more than 1.0 percent of mold spores. FDA notes that an article published in *Rev Franc Allergol* (1980; 20 (4/5):197–201) includes a method for determining pollen contamination by microscopic particle count. A copy of an English translation of this method has been placed on file with the Dockets Management Branch and will be furnished to each licensed manufacturer of allergenic extracts. FDA considers this method, or a similar method that may be satisfactory but different, to be appropriate for determining pollen contamination. FDA advises that it has already amended § 680.1(b) by adding new §§ 680.1(b)(2) and 680.1(b)(3)—see **Federal Register** of June 21, 1984 (49 FR 25430).

FDA interprets the Panel's recommendation that allergens in food extract source material be free of nonspecific irritants to reflect the Panel's concern with the presence in source materials of pesticides or of substances that may be more highly allergenic and produce false reactions. FDA believes that the food extract source material must be of a quality suitable for human food and be collected and processed in a manner to avoid contamination with such substances.

FDA disagrees with the Panel's recommendation for a maximum storage time limit of 5 years for dried source material. FDA believes that the storage time limit should not be set arbitrarily; rather, it should be based on stability studies performed on each product.

E. Manufacturing

1. The Panel recommended that manufacturers maintain standard operating procedures and records of manufacture and testing consistent with FDA regulations and requirements for licensure.

FDA agrees. These written procedures and records should be maintained by licensed manufacturers in accordance with CGMP's (21 CFR Part 211) and are subject to FDA inspection at least once every 2 years during regular business hours unless otherwise directed (21 CFR 600.12 and 600.21). See **Federal Register** of June, 7, 1983; 48 FR 26313. (Also see item D.3. above concerning source materials.)

2. The Panel recommended that manufacturers use known procedures that enhance stability. Further, where potency standards are available, the dating period must be verified by appropriate stability testing.

FDA agrees with this recommendation. Sections 211.137 and 211.166 of the CGMP's concerning expiration dating and stability testing, respectively, include specific requirements for allergenic extracts which are consistent with the stability testing recommendations of the Panel. The dating period for extracts without potency standards is specified under § 610.53 (21 CFR 610.53).

3. The Panel recommended that culture media into which organisms are inoculated to manufacture allergenic extracts contain no allergenic substances other than those necessary as a growth requirement.

FDA notes that this recommendation is consistent with § 680.2(b) (21 CFR 680.2(b)). The agency believes that manufacturers should try to comply with this requirement. FDA recognizes, however, that it may not be possible in all cases for a culture medium to be completely free of allergenic substances that are not necessary as a growth requirement. Accordingly, FDA is proposing to amend § 680.2(b) to provide that, if culture media must contain allergenic substances other than the labeled allergen, such substances must be identified in the license application and in the "Description" section of the package insert.

4. The Panel recommended that liquid products intended for oral administration that are filled in multiple-dose final containers contain a preservative in a concentration adequate to inhibit microbial growth.

FDA agrees with this recommendation which is consistent with the existing requirement under § 680.2(c) (21 CFR 680.2(c)).

5. The Panel recommended that products contain no more residual pyridine in the final product than 25 micrograms per milliliter.

FDA agrees. This recommendation is consistent with § 680.2(d) (21 CFR 680.2(d)), and no change in the regulations is necessary.

6. The Panel recommended that final containers of extracts for diagnostic use be no larger than sufficient to deliver 5 milliliters and that other final containers for extracts be no larger than sufficient to deliver 30 milliliters.

In the **Federal Register** of July 14, 1978 (43 FR 30302), FDA published a proposed regulation to limit the maximum volume of allergenic extract in multiple-dose containers to 30 mL. Following publication of the proposal, the agency reviewed data not previously available which demonstrated no relationship between product volume and risk of product contamination. Accordingly, in the **Federal Register** of August 30, 1983 (48 FR 39243), the proposal was withdrawn. Pending the availability of data which demonstrate conclusively that large volumes of extract in containers affect adversely the suitability of the product, FDA will continue to permit the use of large-volume containers for allergenic extracts.

F. Mixed Extracts

1. The Panel recognized diagnosis using fixed-combination extract mixtures as an acceptable procedure under certain limitations. The Panel recommended that such mixtures, standardized for each component, be placed in regulatory categories corresponding to the categories recommended for the individual components.

FDA believes that the potency of mixture must ultimately be established. FDA notes that no extract that may be removed from the market as a result of its classification into a particular regulatory category will be permitted to be used as a component in a mixture. A fixed-combination extract is subject to the specifications under § 601.25(d)(4).

2. The Panel recommended that labeling of a mixture for diagnosis include instructions for interpretation of the test and cautions concerning excessive reactions to the mixture.

FDA agrees with this recommendation and advises that § 201.57 provides for such instructions and cautions. If it is necessary for a manufacturer to update or revise its labeling accordingly, the proposed changes shall be submitted to, and reviewed by, the Office of Biologics Research and Review in accordance with § 601.12.

3. The Panel recommended that no more than 5 to 10 components be included in a mixed extract.

FDA disagrees with this recommendation at this time. The agency agrees with the logic of the Panel's discussion related to the disadvantages of diagnosis and therapy using mixed extracts with many individual components. However, the agency concludes that the present scientific data are not adequate to publish regulations establishing a valid limit on the number of components in a mixture. Accordingly, the agency is not proposing such limits at this time.

4. The Panel recommended the use of mixed extracts for immunotherapy, provided the mixture contains only those allergens to which the patient is clinically sensitive and the quantity of each allergen is sufficient to ensure an adequate dose. The Panel also recommended that fixed-combination extracts not be used for therapy (which would in effect limit the use of extract mixtures for therapy to those mixtures prepared to a physician's prescription).

FDA agrees that a mixed extract for therapy should contain only those allergens to which the patient is clinically sensitive, and the quantity of each allergen should be sufficient to ensure an adequate dose. FDA does not agree that mixed extracts for therapy must, without exception, be limited to mixtures prepared by a physician's prescription. However, consistent with the Panel's recommendations (accepted by FDA) concerning patient sensitivity and adequate dosage, FDA is proposing that a mixture be used for therapy only for those patients who are sensitive to each allergen (component) of the mixture. (Also see item F.5. below.)

5. The Panel recommended that labeling of mixtures for immunotherapy should: (1) Note that the occurrence of excessive reactions to a mixture should be investigated to identify the responsible component; (2) include cautions that the patient should not receive extracts of a substance to which he is neither reactive on skin testing nor clinically sensitive, and (3) alert the physician to the possibility that the patient may become sensitized to components of the mixture to which the patient was not previously sensitive.

FDA agrees with these labeling recommendations concerning mixtures

for immunotherapy. Such labeling recommendations are consistent with other recommendations by the Panel concerning the therapeutic use of extract mixtures. Therefore, FDA proposes that the product labeling for mixed extracts be revised accordingly.

G. Standardization

1. The Panel made many general recommendations regarding the standardization of allergenic extracts consistent with current and projected scientific knowledge and technology. Because very few allergens have been isolated in a relatively pure state, the Panel qualified many of its recommendations concerning standardization of products and components with phrases like "whenever possible," "when feasible," "as soon as parcticable," and "as is consistent with current knowledge." The Panel recommended procedures, particularly concerning potency and identity, for many specific products, including those utilizing adjuvants, that may be useful for standardization of a batch of extract or of final container material. The potency of allergenic extracts should ultimately be measured not only product-by-product, but also component-by-component.

FDA is aware that imposing requirements for stringent standards of purity and potency, without regard to the limited scientific knowledge available, would severely restrict the number of allergenic extracts supplied for physicians and the public and may hinder the clinical management of allergenic patients. Accordingly, FDA's ongoing program in the Office of Biologics Research and Review of the Center for Drugs and Biologics for the testing and standardization of allergenic extracts and their components includes workshops for manufacturers and other interested persons on methodology and collaborative testing programs to ensure that the scientific knowledge is available to manufacturers, as such knowledge is developed. FDA has distributed to manufacturers of allergenic extracts the details of several methods of standardization, including isoelectric focusing, RAST, radial immunodiffusion, nitrogen determination, and urushiol determination of oral poison ivy and poison oak products.

As standards are developed for products or components, e.g., antigen E requirements for short ragweed pollen extracts, they will be published in the **Federal Register** as a notice of proposed rulemaking, or, if appropriate, made available to the public as guidelines in accordance with § 10.90(b) (21 CFR 10.90(b)), or be made available to manufacturers who wish to amend their license applications consistent with the ideas and recommendations in the procedures involved.

2. The Panel recommended that FDA: (1) Develop, maintain, and distribute reference preparations to manufacturers and researchers for identity and potency testing of allergenic extracts; (2) establish a minimum level of potency for every allergenic extract product; (3) establish minimum identity standards to ensure the availability of consistent allergenic extract products; and (4) eventually adopt international standards applicable to allergenic extracts.

The Office of Biologics Research and Review has developed and distributed certain reference preparations, e.g., an official U.S. Reference preparation of a short ragweed pollen extract which contains a known quantity of antigen E. The Office of Bilogics Research and Review is developing other reference preparations in collaboration with manufacturers of allergenic extracts. As potency standards or identity standards become available, requirements for minimum levels of potency or identity will be proposed. FDA now requires a minimum content of the antigen E allergen in certain short ragweed pollen extracts (see 21 CFR 680.4). The Office of Biologics Research and Review agrees that development of international standards is a long-range goal the agency should strive to achieve, and it has taken a leading role in international efforts evaluating the establishment or world-wide uniform methodologies and standard preparations for allergenic extracts.

3. The Panel recommended that: (1) The potency of all allergenic extracts be measured by direct skin test reactivity in specifically sensitive individuals using a reference standard for comparison before the first licensing of the product; (2) the human potency results be correlated with the results of in vitro tests such as RAST inhibition, radialimmunodiffusion, or leukocyte histamine release because this correlation would allow the in vitro test to be used to control the potency of subsequent lots of the allergenic extract; and (3) the potency be expressed by proven designations rather than the traditional unreliable units of PNU content and weight-to-volume (W/V).

FDA agrees that skin testing in humans may be among the appropriate tests to be used to determine biological activity before licensure of the product. However, the agency notes that such requirements for licensure will be applied only to products for which reference standards for comparison of reactivity are available. As in vitro tests, such as antigen E determination and RAST, are developed, they will be proposed as official potency tests on finished products with a required level of potency. When a manufacturer obtains approval to use a potency procedure other than the traditional PNU content or W/V, the potency expressed on the label will be the value obtained by the new procedure. The PNU content or W/V may be required for an interim period of time so that users of the products will be able to adjust to using the new potency values.

4. The Panel recommended that biologically active ingredients in allergenic extracts be identified by comparing them to reference standards using isoelectric focusing in gel, crossed immunoelectrophoresis, or some other reliable methods.

FDA agrees that identity testing consistent with §§ 610.14 and 680.1(b) (21 CFR 610.14 and 680.1(b)) should be performed on allergenic extract products and their active components (source materials). As the methods for identity testing become available, they either will be proposed as official tests, or be made available as agency guidelines, or be made available as ideas and recommendations to manufacturers who wish to amend their license applications to include the methods.

5. The Panel recommended that standardized nomenclature be used in labeling, regulating records, and in the scientific literature to make the contents of allergenic extracts more readily discernible to users of the products. The Panel also recommended that the product labeling identify the source material used for the extract in accordance with currently acceptable standard scientific nomenclature.

FDA agrees that standardized nomenclature should be adopted wherever possible, including the labeling of allergenic extracts. Accordingly, FDA is proposing that manufacturers' product labeling be amended to clearly identify the source material used in the manufacture of the final product. In addition, the agency is proposing to amend § 680.1 (a) concerning the proper name and definition of allergenic, extract(s), consistent with the format and text which defines other biological products under the codified additional standards. Concomitantly, FDA is proposing to amend §§ 600.13, 610.15(a), 680.1(b), 680.2(b), and 680.3 (b)(1) and (c) to reflect the change in the proper name of the products.

FDA notes that the Office of Biologics Research and Review has been providing manufacturers of allergenic extracts with new listing forms that provide for the listing by each manufacturer of all products that are produced under an approved license application for allergenic extracts. The purpose of this listing is to promote consistency in nomenclature and establish a computerized listing of each product that is produced by each manufacturer.

6. The Panel recommended criteria for further testing of Category IIIA extracts.

As discussed earlier in this response, the regulations concerning the Category IIIA classification have been changed since the Panel completed its review, and all products recommended for Category IIIA will be reclassified by an advisory review committee into either Category I or Category II. Therefore, the criteria for further testing of these products are no longer applicable, and the agency will publish a separate proposal concerning these products after its review of the advisory committee's future reclassification recommendations.

FDA has carefully considered the environmental effects of the proposed regulation and because the proposed action will not significantly affect the quality of the human environment, has concluded than an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Dockets Management Branch, Food and Drug Administration.

FDA has examined the regulatory impact and regulatory flexibility implications of the proposed regulation in accordance with Executive Order 12291 and the Regulatory Flexibility Act. The agency concludes that 19 allergen manufacturers will be affected by these requirements, of which approximately 14 are small manufacturers. Costs per firm could possible vary from zero to several thousand dollars, depending upon current firm practices, adequacy of current labeling, and the consequences resulting from eventual license revocation of Category IIIB products. The expected costs are insufficient to warrant designation as a major rule under any of the criteria specified under section 1(b) of Executive Order 12291 or to require a regulatory flexibility analysis. Accordingly, under section 605(b) of the Regulatory Flexibility Act, the Commissioner of Food and Drugs certifies that this rulemaking, if promulgated, will not have a significant economic impact on a substantial number of small entities. A copy of the threshold assessment for supporting this determination is on file with the Dockets Management Branch.

List of Subjects

21 CFR Part 600

Biologics.

21 CFR Part 610

Biologics.

21 CFR Part 680

Allergenics.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)), the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)), and the Administrative Procedure Act (secs. 4, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 701–706))), and under 21 CFR 5.11, it is proposed that Subchapter F of Chapter I of Title 21 of the Code of Federal Regulations be amended in Parts 600, 610, and 680, as follows:

PART 600—BIOLOGICAL PRODUCTS: GENERAL

§ 600.13 [Amended]

1. In Part 600, § 600.13 *Retention samples* is amended by changing "Allergenic Products" to read "Allergenic Extracts."

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

2. In Part 610, § 610.15 *Constituent materials* is amended in paragraph (a) by changing "Allergenic Products" to read "Allergenic Extracts."

PART 680—ADDITIONAL STANDARDS FOR MISCELLANEOUS PRODUCTS

3. In Part 680:

a. Section 680.1 is amended by revising the section heading and paragraphs (a) and (b)(1) and by adding new paragraph (b)(4), to read as follows:

§ 680.1 Allergenic Extracts.

(a) *Proper name and definition.* The proper name of this product shall be "Allergenic Extract(s)," which shall be prepared from an allergenic source material and administered to humans for the diagnosis, prevention, or treatment of allergies. The products include those Allergenic Extracts prepared with or without immunological adjuvants as well as extracts of poison ivy, oak, and sumac. The licensed proper name may require modification to reflect a specific characteristic which renders unique properties to the final product.

(b) *Source materials*—(1) *Criteria for source material.* Only specifically identified allergenic source materials which contain no more than 1.0 percent of detectable foreign materials shall be used in the manufacture of an Allergenic Extract, except that molds, animals, and pollens shall meet the requirements under paragraphs (b) (2), (3), and (4) of this section, respectively. Source materials such as feathers, hairs, and danders shall be free from blood and serum.

* * * * *

(4) The amount of foreign materials in pollens shall be determined by a method approved by the Director, Office of Biologics Research and Review. Pollens determined to contain more than 1.0 percent of foreign materials other than mold spores may be used in the manufacture of Allergenic Extracts if the product labeling identifies the assayed amount of contamination in the batch of pollen used to produce the product. Pollens shall contain no more than 1.0 percent of mold spores.

* * * * *

b. Section 680.2 is amended by revising the section heading and paragraph (b), to read as follows:

§ 680.2 Manufacture of Allergenic Extracts.

* * * * *

(b) *Cultures derived from microorganisms.* Whenever possible, culture media into which organisms are inoculated for the manufacture of Allergenic Extracts shall contain no allergenic substances other than those necessary as a growth requirement. If the culture media must contain an allergenic substance other than the labeled allergen, such substance must be identified in the license application and in the "Description" section of the package insert. However, neither horse protein nor any allergenic derivative of horse protein shall be used in culture media.

* * * * *

§ 680.3 [Amended]

c. Section 680.3 *Tests* is amended in paragraph (b)(1) and the introductory text of paragraph (c) by changing "Allergenic Product" to read "Allergenic Extract."

Interested persons may, on or before April 23, 1985, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received

comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret Heckler,

Secretary of Health and Human Services.

[FR Doc. 85-1298 Filed 1-22-85; 8:45 am]

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Wednesday
January 23, 1985

Part III

Department of Agriculture

Rural Electrification Administration

7 CFR Part 1789

Revision and Codification of REA Policies Concerning Audits of REA Borrowers; Proposed Rule

DEPARTMENT OF AGRICULTURE

Rural Electrification Administration

7 CFR Part 1789

Revision and Codification of REA Policies Concerning Audits of REA Borrowers

AGENCY: Rural Electrification Administration (REA) USDA.

ACTION: Proposed rule.

SUMMARY: The Rural Electrification Administration (REA) proposes to amend 7 CFR Chapter XVII, REA Regulations by adding a new part, Part 1789—REA Policy on Audits of Electric and Telephone Borrowers. Current REA policy on this subject is set forth in REA Bulletin 185–1:465–1, Audit of REA Borrowers' Accounting Records, and 185–2:465–2, Audit Working Papers. As part of REA's continuing effort to codify its policies and procedures, this new part is being proposed. In addition to codifying the policies and procedures, REA's audit policy is being updated to reflect pertinent requirements contained in Statements on Audit Standards published by the American Institute of Certified Public Accounts and in Financial Accounting Standards Board's Statements since 1972. Within the last two years, REA has increased its reliance on the audit work performed by independent certified public accountants (CPAs) and upon information contained in CPA's workpapers. In keeping with this effort to rely more on independent CPAs, the rule is being proposed to provide CPAs with more detail on audit procedures and documentation required by REA. Additionally, a revision is being proposed to the existing audit policy that will require REA borrowers to select a CPA who belongs to, or agrees to belong to, an approved peer review program after December 31, 1985. The proposed rule will affect all present and future REA electric and telephone borrowers. Once the proposed rule is published final, REA Bulletins 185–1:465–1 and 185–2:465–2 will be rescinded.

DATE: Public comment must be received by REA no later than: March 25, 1985.

ADDRESS: Submit written comments to Mr. Roland S. Heard, Chief, Technical Accounting and Auditing Staff, Borrower Accounting and Services Division, Rural Electrification Administration, Room 2231, South Building, U.S. Department of Agriculture, Washington, D.C. 20250. All written submissions made pursuant to this action will be made available for public inspection during regular business hours at the above address.

FOR FURTHER INFORMATION CONTACT: Mr. Roland S. Heard, Chief, Technical Accounting and Auditing Staff, at the above address, telephone number (202) 382–8227. The Draft Impact Analysis describing the options considered in developing and implementing the proposal is available on request from the above address.

SUPPLEMENTARY INFORMATION: REA proposes to amend 7 CFR Chapter XVII, REA Regulations by adding a new part, Part 1789—REA Policy on Audits of Electric and Telephone Borrowers. This proposed action has been issued in conformance with Executive Order 12291, Federal Reguation. It will not: (1) Have an annual effect on the economy of $100 million or more; (2) result in major increases in costs or prices for consumers, individual industries, Federal, State, or local government agencies or geographic regions; or (3) result in significant adverse effects on competition, employment, investment or productivity, and therefore has been determined "not major."

This action does not fall within the scope of the Regulatory Flexibility Act. The programs listed in the Catalog of Federal Domestic Assistance that will be reported are 10.850—Rural Electrification Loans and Loan Guarantees and 10.851—Rural Telephone Loan and Loan Guarantees.

Background

REA Bulletins 185–1:465–1 and 185–2:465–2 were issued in 1972 setting out specific auditing and reporting requirements for CPAs auditing REA borrowers. Bulletin 185–1:465–1 was amended in 1978 to include additional reporting requirements on electronic data processing activities and related party transactions, however, no attempt was made to update the Bulletin to include currently generally accepted accounting principles (GAAP) and audit standards (GAAS). Bulletin 185–2:465–2 has never been updated. Therefore, it is necessary to update REA's stated audit policy to include applicable changes in GAAP and GAAS.

In order to reduce government costs, REA has modified the scope of the loan fund audits performed by REA accounts to avoid duplicating audit work performed by CPAs during the annual audit of borrowers' accounting records. Increasing reliance on the work of CPAs auditing REA borrowers requires that REA be assured that quality audits are being performed. One of the most significant recent developments in the public accounting profession has been the emergence of independent peer reviews of a firm's quality control procedures and workpapers by other CPAs or other CPA firms. A peer review program provides a mechanism for evaluating the quality of audit work performed by CPAs auditing REA borrowers. CPAs may join a peer review program through the AICPA, state accounting societies or other associations of public accountants. Currently, 104 of the 538 CPAs auditing REA borrowers participate in the AICPA peer review program. REA is proposing to require peer reviews of all CPAs auditing REA borrowers after December 31, 1985. These peer reviews will be performed by accounting practitioners working in the private sector rather than by government employees. A favorable peer review report will provide reasonable assurance to REA that the independent CPA selected by the borrower has adhered to generally accepted accounting principles and auditing standards. Only in unusual circumstances will it be necessary for an REA employee to review the quality of a CPA's work.

List of Subjects in 7 CFR Part 1789

Loan programs—energy; Loan programs—communications, Telecommunications, Telephone.

In view of the above, REA proposes to add a new part, Part 1789—REA Policy on Audits of Electric and Telephone Borrowers, to 7 CFR Chapter XVII to read as follows:

PART 1789—REA POLICY ON AUDITS OF ELECTRIC AND TELEPHONE BORROWERS

1. Part 1789 is added to read as follows:

Subpart A—General Provisions

Sec.

1789.1 General.
1789.2 REA requires annual audits.
1789.3 Borrowers required to have annual audits.
1789.4 Borrowers' responsibilities.
1789.5 Qualifications of CPAs.
1789.6 Scope of audit.
1789.7 Audit date.
1789.8 Access to audit working papers.
1789.9 Audit requirements of other mortgages.

Subpart B—Selection of CPA and REA Approval

1789.15 Board of Directors responsible for selection.
1789.16 Audit agreement.
1789.17 Notification of selection.
1789.18 Approval of CPA.

Subpart C—Submission and Review of Audit Report

Sec.
1789.25 CPA's submission of the audit report.
1789.26 Borrower's review and submission of audit report.
1789.27 REA review of audit report.

Subpart D—Audit Reporting Requirements

1789.30 General.
1789.31 Financial statements and accompanying notes.
1789.32 Management letter.

Subpart E—Audit Procedures and Documentation

1789.35 Audit Standards.
1789.36 Evaluation of audit working papers by REA.
1789.37 Planning and supervision.
1789.38 First annual audit.
1789.39 Audit documentation.

Appendix A—Sample Audit Report for Electric Distribution Cooperative
Appendix B—Sample Audit for Class A or B Commercial Telephone Companies
Appendix C—Sample Management Letter (Electric or Telephone).

Authority: U.S.C. 901 et seq.

Subpart A—General Provisions

§ 1789.1 General.

This part sets out policy of REA on the selection and retention of independent certified public accountants (CPAs) to perform annual audits, auditing and reporting requirements for CPAs selected to perform audits of REA borrowers, and documentation standards for work done in connection with audit reports prepared for REA borrowers.

§ 1789.2 REA requires annual audits.

(a) *Audit Requirement.* REA requires that borrowers have their financial records audited annually by CPAs selected by the borrowers and approved by REA. An annual audit, short-form audit report and accompanying management letter prepared in accordance with Subpart D meet the requirements of Article II of the REA mortgage.

(b) *Definition of Audit.* Audit, as used in this part, refers to an examination of financial statements by an independent CPA for the purpose of expressing an opinion on the fairness with which those statements present financial position, results of operations and changes in financial position in conformity with generally accepted accounting principles. A report prepared in connection with a review or compilation of financial statements as defined in Statement of Standards for Accounting and Review Services No. 1, *Compilation and Review of Financial Statements,* does not satisfy the requirements of the REA mortgage. Additionally, an audit report as described in Statement of Audit Standards No. 14, *Special Reports,* does not satisfy the mortgage requirements.

§ 1789.3 Borrowers required to have annual audits.

All borrowers which have received their first advance of loan funds shall have an annual audit by a CPA unless a waiver is granted by REA. Thereafter, borrowers are required to provide an annual audit as long as they are subject to Article II of the Mortgage.

§ 1789.4 Borrowers' responsibilities.

REA borrowers are responsible for:

(a) The selection of a qualified CPA as set out in § 1789.5, and

(b) The submission of the required audit report and management letter as set out in § 1789.26.

§ 1789.5 Qualifications of CPAs.

(a) *Certification.* The accountant auditing the books and records of an REA borrower shall be a CPA of some state, territory or the District of Columbia. The CPA does not have to be licensed by the state in which the borrower is located; however, they are required to abide by the rules and regulations of professional conduct promulgated by the accountancy board of the state in which the borrower is located.

(b) *Independence.* The CPA selected to perform the audit shall be independent. A CPA who has or has had any direct financial interest or any material indirect financial interest with the borrower during the period covered by the audit is not considered independent. Additionally, a CPA will not be considered independent as defined in the American Institute of Certified Public Accountants' (AICPA) *Code of Professional Ethics,* if he or she is, or was during the period under audit, connected with the borrower as a promoter, underwriter, trustee, director, officer or employee.

(c) *Participation in a peer review program.* Any CPA who audits an REA borrower after December 31, 1985 is required to belong to an approved peer review program.

(1) *Acceptable peer review programs.* CPAs may elect to participate in one of the following peer review programs:

(i) *The peer review program conducted by the AICPA's Division for CPA Firms.* CPA firms may belong to either the Private Companies Practice Section or the SEC Practice Section.

(ii) *Independent peer review programs subject to REA approval.* An independent peer review program will generally be approved if it is structured according to the "Standards for Performing and Reporting on Peer Reviews" as published in the AICPA's Division for CPA Firms Private Companies Practice Section, *Peer Review Manual* or the SEC Practice Section, *Peer Review Manual.*

(2) *Notification.* The CPA shall notify the Director, Borrower Accounting and Services Division (BASD), REA, 14th and Independence Ave., SW., Washington, D.C. 20250, by March 1, 1986, of participation in an approved peer review program. REA will notify the CPA within 60 days if the peer review program selected is unacceptable and the reasons therefore.

(3) *Submission of reports.* The CPA shall submit a copy of any peer review report and accompanying letter of comment, if any, within 60 days of date of receipt by the CPA. If the peer review report indicates a followup review will be made, the CPA is required to submit subsequent reports. Usually peer review reports shall be submitted to REA at least once every three years, or more frequently, if required by the peer review program.

§ 1789.6 Scope of audit.

(a) The scope of the audit shall be established in accordance with generally accepted auditing standards issued by the American Institute of Certified Public Accountants.

(b) The CPA shall perform an examination of the financial statements and tests of transactions sufficient to enable him or her to express an opinion on the financial statements. The borrower shall not limit the audit to an extent that the CPA is unable to meet REA's audit requirements or provide an unqualified opinion as to the fairness of the financial statements. REA does not accept an audit report in which the CPA has qualified the opinion due to limitations placed on the examination. If the CPA determines during the audit that an unqualified opinion cannot be issued due to scope limitations, the CPA shall immediately contact the Director, Borrower Accounting and Services Division (BASD), REA, 14th and Independence Ave., SW., Washington, D.C. 20250.

§ 1789.7 Audit date.

The annual audit may be performed as of the end of any calendar month. Audits are to be performed as of the end of the same date each year unless prior approval to change the date is obtained from REA. Borrowers may request a change in audit date by writing to the appropriate area office. A change in

audit date will not be approved unless the audit report with the new "as of" date meets all reporting requirements in Subpart D.

§ 1789.8 Access to audit working papers.

CPAs performing audits of REA borrowers under the provisions of this part shall make the audit working papers, or certified copies thereof, available to REA upon request.

§ 1789.9 Audit requirements of other mortgagees.

Some borrowers have a common mortgage and security agreement with REA and other mortgagees. Usually these mortgages require that the borrower have their accounts and supporting records audited annually by a CPA selected by the borrower and satisfactory to the mortgagees. Audit reports are required to be furnished by the borrower to the mortgagees in a form and substance satisfactory to them. Provision is also made for reasonable access to and inspection of the borrower's records by the mortgagees.

Subpart B—Selection of CPA and REA Approval

§ 1789.15 Board of Directors responsible for selection.

(a) *Selection.* The borrower's board of directors or an audit committee composed of only board members is responsible for selecting a properly qualified CPA. In selecting a CPA the board of directors should consider the qualifications of CPAs available to do the work, with particular regard to experience in performing audits of utilities and the ability to complete the audit and submit the report to the borrower within three months of the "as of" date of the audit.

(b) *Board Resolution.* The board's selection of a CPA to perform the annual audit should be recorded by a board resolution. The resolution should state that the CPA selected meets REA qualifications to perform an audit and will provide an audit agreement.

§ 1789.16 Audit agreement.

(a) An annual audit agreement prepared by the borrower's CPA and signed by the CPA and the borrower shall provide assurance that the conditions of this section will be met by the CPA.

(1) The audit report will be signed by a certified public accountant or firm of certified public accountants in good professional standing with the state licensing board.

(2) The CPA is independent as defined and interpreted by the Professional Ethics Division of the AICPA.

(3) The CPA belongs to an approved peer review program.

(4) The CPA agrees to comply with the Professional Standards (generally accepted auditing standards) and the *Code of Professional Ethics* of the AICPA, as though a member.

(5) The audit will be performed and the audit report and management letter will be prepared in accordance with REA requirements outlined in Subpart D.

(6) The audit report and management letter with copies for transmittal to REA, and supplemental lenders, if applicable, will be submitted to the board of directors within three months of the "as of" date of the audit.

(7) Documentation and evidence of audit work performed will be prepared in accordance with the professional standards of the AICPA and REA requirements.

(8) Audit workpapers or certified copies thereof will be made available to REA as requested.

(b) The audit agreement may cover additional conditions or items not listed in paragraph (a) of this section.

(c) A copy of the annual audit agreement shall be available at the borrower's office for inspection by REA personnel.

§ 1789.17 Notification of selection.

(a) When the selection has been made, the borrower shall advise REA and supplemental lenders, if applicable, by letter of its selection.

(b) Notification to REA and supplemental lenders, if applicable, that the same CPA has been selected for succeeding annual audits of the borrower's records is not required; however, the procedure must be followed for each *new* CPA selected, even though the new CPA may previously have been approved to audit records of other REA borrowers. Changes in the name of a CPA firm are considered to be a change in a CPA.

§ 1789.18 Approval of CPA.

(a) The notification of the selection must reach REA and supplemental lenders, if applicable, at least 15 days before the audit is to begin. If the borrower's selection of a CPA is not satisfactory to REA, or a supplemental lender, the borrower shall be advised within this period. In the absence of any notice to the contrary, the selection shall be deemed to have REA approval.

(b) Failure to meet generally accepted accounting standards, failure to comply with REA's specific auditing and reporting requirements, or a change from the CPA's independent status shall generally result in a determination that the audit report does not meet REA requirements and does not satisfy the requirements of Article II of the mortgage.

Subpart C—Submission and Review of Audit Report

§ 1789.25 CPA's submission of the audit report.

(a) *Time Limit.* As soon as possible after completion of the audit but within three months of the "as of" date, the CPA shall deliver the audit report and the management letter to the president of the board of directors. As a minimum, copies should be provided for each member of the board of directors, the manager, two copies for REA, and one copy for each supplemental lender.

(b) *Presentation to Board.* In addition to providing sufficient copies of the report and management letter for each member of the board, the CPA should report the audit findings orally to the board of directors at the completion of the audit.

§ 1789.26 Borrower's review and submission of audit report.

(a) The board of directors should note and record receipt of the audit report and any action taken in response to the report in the minutes of the board meeting at which the report is presented.

(b) The borrower shall forward two copies of the audit report and management letter to REA within four months of the audit date. One copy of the same information is to be forwarded to supplemental lenders, where applicable, within the same time limit.

(c) The borrower shall furnish REA and supplemental lenders with copies of each special report, summary of recommendations or similar communications, if any, received from the CPA as a result of the audit.

§ 1789.27 REA review of audit report.

(a) REA shall review the audit report and management letter for information relating to the borrower's operations and financial status. The audit report and management letter shall also be reviewed for conformance with the auditing and reporting requirements set out in Subpart D.

(b) After its review, REA shall furnish the borrower with any comments or recommendations which it may have. A copy of these comments shall also be sent to the CPA and supplemental lenders, if applicable.

Subpart D—Audit Reporting Requirements

§ 1789.30 General.

The CPA shall:

(a) Present a short-form audit report of the type illustrated in Appendices A and B of this subpart to the borrower. The financial statements and opinion regarding these statements should be in accordance with generally accepted accounting principles and audit standards.

(b) Provide a management letter to the borrower as illustrated in Appendix C. Comment on all significant deficiencies disclosed during the course of the audit, and, where appropriate, make recommendations for changes necessary to eliminate the deficiencies.

(c) Deliver the audit report and management letter (with copies required in § 1789.25) to the borrower as soon as possible after completion of the audit but not more than three months after the "as of " date.

§ 1789.31 Financial statements and accompanying notes.

(a) *Electric borrowers.* The CPA shall present a comparative balance sheet, statement of revenue and patronage capital and statement of changes in financial position. The auditor's report shall cover all statements presented. Suggested formats for these statements are shown in Appendix A.

(b) *Telephone borrowers.* The CPA shall present a comparative balance sheet, statement of income and retained earnings (or patronage capital, if appropriate) and statement of changes in financial position. The auditor's report shall cover all statements presented. The suggested formats for these statements are shown in Appendix B.

(c) The CPA shall provide adequate disclosure in the notes to the financial statements on the following items:

(1) Significant accounting policies.

(2) Depreciable assets (property, plant and equipment) and depreciation rates.

(3) Assets subject to lien.

(4) Investments.

(5) Leases.

(6) Long-term debt.

(7) Pension and retirement plans.

(8) Contingent liabilities.

(9) Related party transactions.

(10) Material subsequent events.

(11) Unusual accruals and allowances.

(12) Prior period adjustments.

(13) Where applicable, additional disclosures specified in generally accepted accounting principles and audit standards necessary to allow readers to use, understand and interpret the financial statements.

§ 1789.32 Management letter.

In accordance with REA reporting requirements the CPA shall prepare a management letter specified in this subpart. This management letter shall clearly identify the items covered in the review; indicate whether the review included tests of the compliance with the procedures covered by the review, and state the CPA's conclusions concerning the adequacy of the procedures studied. REA requires the CPA to report all conditions noted during the audit that are not in conformance with REA's specified policies and procedure. The CPA shall specifically cover and report on the following items:

(a) Provide a statement that the examination procedures specified in Part 1789 have been performed.

(b) *Internal control.* (1) Give an evaluation of the effectiveness and reliability of the system of internal accounting controls and outline any recommendations for improvement. Comments provided shall: (i) Clearly identify the areas covered by the study, (ii) indicate whether the study included tests of compliance with the procedures covered by the study, and (iii) state the CPA's conclusions and identify material deficiencies in the borrower's internal control noted during the review. Statement on Auditing Standards No. 30, paragraph 49, gives an example of a report on internal accounting control which may be used. However, the additional requirements stated here must be included in the report.

(2) If electronic data processing systems are in use, a statement as to the effectiveness and reliability of those systems is also required. The review and evaluation should be in accordance with Statement on Auditing Standards No. 48, *The Effects of Computer Processing on the Examination of Financial Statements.* If electronic data processing systems are not in use, so state.

(c) *Accounting and records.* Comment on the adequacy and effectiveness of the reporting and accounting procedures, discuss the general condition of the records, and outline any recommendations for improvement. Include comments on the adequacy and fairness of the methods used in accounting for labor, material and overhead, and the distribution of these costs to construction, retirement, and maintenance or other expense accounts. Where inadequate accounting or records are noted, comments should be included on matters such as:

(1) The degree of inadequacy of work order procedures in use in accumulating and recording accurate costs of new construction, replacements, and retirements.

(2) Whether subsidiary plant records agree with the controlling general ledger plant accounts.

(3) Whether construction clearing accounts are cleared promptly of costs of completed construction to the proper classified plant accounts and whether depreciation was accrued on such completed construction from the dates completed plant was placed in service.

(4) Whether retirements of plant are currently and systematically recorded and properly priced.

(5) Whether all costs associated with retirements of plant are properly accounted for in the accumulated provisions for depreciation accounts and comments on any unusual charges or credits to such accounts.

(6) When REA approval was not obtained for a sale requiring such approval, and when receipts from sales of plant, material, or scrap were not handled in conformance with REA requirements.

(d) *Material control.* Comment on the adequacy of the control over material and supplies. When appropriate, comment on discrepancies between physical inventory, perpetual inventory records, and general ledger balance, including dollar amount of discrepancy, and disclose the disposition of any major differences. Include recommendations for disposition of deferred amounts remaining on the books at the close of the audit for which a satisfactory method of disposition has not been determined.

(e) *Compliance with loan documents.* Except for municipalities or public utility districts, state whether provisions of the loan documents have been complied with.

(f) *Reports to REA.* State whether the information in the December 31 financial reports (Form 7 or Form 12—Electric or Form 479—Telephone) submitted to REA is in agreement with the borrower's records. Comment on any exceptions noted. If an amended report has been filed as of December 31, the comments shall relate to the amended report.

(g) *Service contracts.* If management, operations, or billing services to the borrower are provided by affiliates or others, state whether the payments are in accordance with the service contract. If such services are not provided, a statement to this effect shall be included in the management letter.

(h) *Deposits.* State whether funds in banks and savings and loan associations are in institutions insured by an agency of the Federal government. Also state whether temporary

investment of loan funds is in accordance with REA Bulletin 26–1:327–1 or Bulletin 103–9:405–4, as appropriate.

(i) *Income tax status.* For cooperative borrowers, state whether 85 percent or more of the income is received from members, whether exemption from Federal income tax has been obtained, and whether Internal Revenue Form 990 is being filed annually.

(j) *Related party transactions.* A statement to th effect that all related party transactions have been disclosed in the notes to the financial statements in accordance with Financial Accounting Standards Board Opinion No. 57 *Related Pary Disclosures,* is required. If there were no related party transations during the audit period, so state.

(k) *Sale of plant.* Provide information on sales of plant if REA approval was not obtained where required.

(l) *Depreciation rates.*(1) Comment when the depreciation rates used in computing monthly accruals have not been accepted by the regulatory body having jurisdiction over the borrower. (Electric: In the absence of state or federal regulation, when the rates of depreciation used are not in accordance with REA Bulletin 183–1, Depreciation Rates and Procedures, and have not been specifically approved by REA.

(2) Provide information in the management letter when proper accounting has not been carried out for original costs of plant removed and related salvage, and when the net result of these retirements is not properly reflected in the provision for depreciation accounts. Any unusual charges or credits should be fully disclosed.

Subpart E—Audit Procedures and Documentation

§ 1789.35 Audit standards.

(a) Audits are to be performed in accordance with generally accepted auditing standards adopted by the American Institute of Certified Public Accountants and incorporated in *Standards for Audit of Governmental Organizations, Programs, Activities and Functions* issued by the Comptroller General (1981). This subpart details minimum audit procedures to be performed by the CPA during the examination of the REA borrower's records. However, it is not intended that the requirements specified preclude or limit other audit tests. In accordance with generally accepted auditing standards, the CPA shall exercise judgment in determining additional or alternative auditing procedures necessary to afford a reasonable basis for an opinion.

(b) If an audit test outlined in this subpart was not performed, the CPA shall indicate on the audit program or in the working papers the reason for eliminating the test and note alternate tests performed to satisfy the audit objectives.

§ 1789.36 Evaluation of audit working papers by REA.

(a) CPA audit working papers are periodically reviewed to determine compliance with generally accepted audit standards and REA audit requirements as described in the Part.

(b) CPA will be informed of the results of the review by REA. If serious deficiencies are noted, the letter will detail specific recommendations for improvements and indicate that a follow-up visit will be made to determine compliance with REA requirements. The CPA is required to respond to the evaluation letter within 60 days.

(c) If serious deficiencies are noted in a review of the CPA's working papers, REA will take one of the following actions:

(1) The CPA will be advised that REA borrower clients are being notified that unless REA audit requirements are met, approval to audit REA borrowers will be withdrawn;

(2) The CPA will be prohibited from acquiring additional REA borrowers as clients until REA's auditing requirements are met; or

(3) The CPA will be advised that approval to audit REA borrowers is being withdrawn.

(d) At the exit conference, the CPA will be advised of the possible steps that can be taken. However, the decision of what action will be taken will be made by the Director, BASD.

§ 1789.37 Planning and supervision.

In accordance with Statement on Auditing Standards No. 22, *Planning and Supervision*:

(a) The CPA should have or obtain a level of knowledge of the utility business that will enable him or her to plan and perform the examination in accordance with generally accepted auditing standards.

(b) In planning the examination the CPA should consider the nature, extent and timing of work to be performed and shall prepare a written audit program. This program should set forth in reasonable detail, the audit procedures that the accountant believes are necessary to accomplish the objectives of the examination.

(c) The CPA should review work performed by assisting auditors to determine whether it was adequately performed and that the results are consistent with the conclusions presented in the audit report and management letter.

§ 1789.38 First annual audit.

In accordance with generally accepted auditing standards, REA requires the CPA to obtain sufficient competent evidential matter to afford a reasonable basis for expressing an opinion on *comparative* financial statements he or she has been engaged to examine as well as on the consistency of the application of accounting principles in that year as compared with the preceding year. Statement on Auditing Standards No. 7, *Communications Between Predecessor and Successor Auditors,* provides guidance to CPAs when a change in auditors takes place. REA requires that the first year's working papers detail how the successor auditor complied with SAS No. 7.

§ 1789.39 Audit documentation.

(a) *Internal control.* (1) REA requires the CPA to review the borrowers' internal control procedures in order to form a basis for comments in the management letter. Supporting documentation can be an internal control questionnaire or narratives. Conclusions drawn as a result of this review must be noted in the working papers.

(2) If the CPA does not intend to rely on the borrower's internal control procedures during the audit, a statement of this fact, and the reasons therefore, shall be included in the audit working papers. *However,* if the CPA intends to rely on the borrower's internal control procedures during the audit the following documentation is required:

(i) To support the review of the borrower's system of internal control, the CPA shall document the client major accounting procedures including cash receipts and disbursements, revenue and billing, purchasing, plant accounting, handling of material and supplies and payroll. The documentation shall indicate: (A) The major operating procedures being followed; (B) the flow of information from the initiation of the transaction through the posting of accounting records; (C) key accounting documents processed; (D) the segregation of duties; and (E) authorization limits and approvals required for transactions processed. The narratives may be supported with copies of forms and related flow charts.

(ii) The CPA shall provide in the current audit files: (A) An overall evaluation of the strengths and weaknesses of the client's system of controls; (B) workpapers documenting the tests made to verify that the client's stated procedures were in fact being followed; and (C) documentation indicating those aspects of internal control on which the auditor intends to rely for limiting tests of account balances.

(iii) Where applicable, compliance with Statement on Auditing Standards No. 48, *The Effects of Computer Processing on the Examination of Financial Statements* shall be shown.

(b) *Review of minutes and legal documents.* (1) The working papers prepared by the CPA shall contain extracts from the minutes of the Board of Directors and the annual membership or stockholders' meeting. Copies or outlines resulting from a review of documents such as the articles of incorporation, bylaws, commission orders, mortgages, pension and retirement plans, labor agreements and important contracts are to be a part of the working paper files.

(2) Compliance with transactions authorized in the minutes and with the legal documents noted above shall be tested by the CPA and documented in the working papers.

(c) *Working trial balance.* Amounts on the working trial balance must be readily traceable to audit working papers and to the summarized financial statements included in the audit report.

(d) *Utility plant and depreciation reserves*—(1) *General.* Because of the large proportion of the plant value to total assets, audit of these accounts shall include a thorough examination of additions, replacements, retirements, and changes. Specifically, documentation prepared by the CPA shall show that:

(i) Direct labor and material transactions were reviewed and tested in determining that the client's accounting records reflect a complete accumulation of costs.

(ii) Indirect costs and overhead charges were reviewed, tested and evaluated to determine if they conform to Uniform System of Accounts requirements.

(iii) Costs of completed construction and retirements are cleared promptly from work in progress accounts to classified plant in service and related depreciation reserves.

(iv) Direct purchases of special equiment and general plant were tested and vouched.

(v) Tests were performed to assure accuracy and control of pricing retirements, including tests of salvage and removal costs.

(vi) The borrower's work order procedures were documented and tested.

(vii) Depreciation rates were tested for adequate support, compared to REA guidelines and determined to be in compliance with approved rates.

(2) *Construction work in progress.* (i) The working papers shall include a summary of open work orders reconciled to the general ledger. The CPA should note on the summary unusual or nontypical projects.

(ii) For each annual audit the CPA is required to test a representative number of work orders. It is recommended that, on a test basis, the CPA select at least one month's activity and verify all charges to the work orders by reviewing supporting records. These tests shall cover:

(A) *Equipment purchases.* Review equipment purchases charged to work orders, including payments and receiving reports.

(B) *Contract payments.* Review contracts showing scope of work, nature of contract, contract amount and schedule of payments. Review supporting documents to determine that all services contracted for were in fact rendered.

(C) *Labor.* Select several employees who made a partial allocation of their time to the work orders selected for testing. Review time cards and pay rates for these employees.

(D) *Transportation clearing.* Select several transportation charges assigned to the work order. Review the functions of those individuals assigned to the transportation equipment.

(E) *Material and Supplies.* Review the nature of material and supplies issued to the project and trace amounts and quantities to supporting documents. Review the reasonableness of clearing rates for assignment of stores expense to the work order.

(F) *Overheads.* Review the accuracy of the computation of overheads applied to the work order.

(G) *Other Charges.* Review other costs charged to the work order for support and propriety.

(iii) If construction was not peformed by force account, the CPA shall select a representative number of completed contracts for review. Tests performed shall include:

(A) Schedule payments to contractor and trace to verification of payment and supporting invoice.

(B) Trace contract costs to final close-out documents and to general ledger and continuing property records.

(C) Verify costs of owner furnished materials, if applicable.

(iv) The CPA shall review the borrower's procedures for unitization and classification of work order and contract costs. These tests shall cover:

(A) Tabulation of record units for construction from work order staking sheets to tabulation of record units, to unitization sheets and to continuing property records.

(B) Procedures for unitizing and distributing costs of completed construction to plant accounts.

(C) In the case of electric borrowers, verification that standard costs are being used and test the basis for determining standard costs.

(D) Determination that costs of completed construction are cleared promptly from work in progress accounts.

(3) *Continuing property records.* The CPA is required to determine whether subsidiary plant records agree with the general ledger control accounts, note differences in the working papers and comment on discrepancies in the management letter.

(4) *Retirement work in progress.* The CPA's working paper shall show that tests were made to determine that retirements of plant are currently and systematically recorded, priced on the basis of continuing property records, and that the costs of removal have been properly accounted for. If continuing property records have not been established, the CPA is required to explain the method used in computing costs of units of plant retired and state whether costs appear reasonable. The CPA is also required to test accounting for net loss due to retirement and trace clearing entries to the depreciation reserve, the plant accounts and continuing property records.

(5) *Depreciation reserve.* The CPA's working papers shall include an analysis of transactions for the period and additional working papers showing:

(i) A test of the depreciation provision, including the depreciation base.

(ii) The basis of the depreciation rates. Indicate any change in rates and the reason therefor and, as appropriate, approval by the regulatory body having jurisdiction.

(iii) A test of salvage and removal costs.

(iv) A test for unrecorded retirements.

(6) *Other reserves.* The CPA's working papers shall include an account analysis and tests of transactions for all other material plant reserves, such as the reserve for the amortization of plant acquisition adjustments.

(7) *Narrative.* The CPA shall prepare and include in the working papers a comprehensive narrative on the scope of work done, observations made, and conclusions reached. Specific matters that are to be covered in this narrative include:

(i) The nature of construction and other additions.

(ii) The control over, and the accuracy of pricing retirements.

(iii) The accuracy of distributing costs to classified utility plant accounts.

(iv) An evaluation of the method of: (A) Capitalizing the direct loadings on labor and material costs, (B) distributing transportation costs and other expense clearing accounts and (C) capitalizing overhead costs.

(v) The tests of depreciation.

(vi) Review of agreements such as those relating to acquisitions, property sales, and leases which affect the plant accounts.

(vii) Notations, if applicable, of REA approval in connection with property sales and the propriety of the disposition of the proceeds.

(e) *Cash.* The CPA shall prepare working papers showing that the following audit procedures have been performed:

(1) Tests were performed to ascertain that all significant sources of cash receipts and disbursements are under effective accounting control.

(2) Receipt and disbursement activity was tested for a selected period based upon controls identified.

(3) Cash on hand and working funds were properly counted or confirmed.

(f) *Investments.* The CPA shall prepare working papers showing that the following audit procedures have been performed:

(1) Ownership of investments was verified by inspection or confirmation, as appropriate, and that the securities were properly safeguarded.

(2) Significant transactions (purchases and sales) were examined for proper authorization, approval and supporting documentation and were accurately recorded in the accounting records.

(3) Tests were made of the related income, gain/loss and discount/premium accounts.

(g) *Receivables and Accumulated Provision for Uncollectible Notes and Accounts.* The CPA shall perform and document the audit procedures listed below:

(1) Reconcile the totals of the individual general ledger account balances with the supporting subsidiary detail.

(2) Confirm selected receivables and note in the working papers: (i) The basis of selecting positive and negative confirmation requests and the extent of coverage in each case, and (ii) the results of the confirmation procedures and extent of follow-up on exceptions and nonresponses.

(3) Check thoroughly into any unreconciled differences resulting from requests for confirmation or between subsidiary records and control accounts.

(4) Test cash receipts and recording of revenues in connection with the collection of receivables from original source documents through the general ledger entry.

(5) In testing the reserve for uncollectible notes and accounts provide: (i) A summary analysis of the transactions in the reserve accounts for the audit period; (ii) an evaluation of the adequacy of the accumulated provision for uncollectible notes and accounts; and (iii) evidence that write-offs were properly authorized.

(h) *Material and supplies.* In connection with the inventory of material and supplies the CPA shall perform and document the audit procedures listed below:

(1) Review and comment on the adequacy of the client's inventory procedures. Test check the unit prices, computations and footings on the inventory tabulations. If not present when the inventory was taken, physically count a representative number of items and test check them to the physical inventory records.

(2) Review transactions occurring between inventory count dates and the "as of" audit date.

(3) Ascertain that the perpetual inventory records and the ledger accounts were brought into agreement with the physical inventory and comment on any material discrepancies between the physical inventory records and the general ledger balances.

(4) Test the client's procedures for handling material and supplies. Tests shall cover:

(i) Clerical accuracy of extensions on stock record cards.

(ii) Substantiation of the cost used in pricing.

(iii) Purchases and receipts for a selected period.

(iv) Issuances.

(v) Salvage entries and adjustments.

(5) Review inventory for obsolete items and note conclusions in working papers.

(i) *Other assets*—(1) *Prepayments.*

(i) *Insurance.* The CPA's working papers shall contain an analysis of transactions, together with evidence that:

(A) A representative number of transactions were reviewed for support.

(B) The method of amortization was tested.

(C) Underlying insurance policies and REA Form 55s were examined.

(2) *Deferred charges*—(i) *Extraordinary retirement losses.* The CPA's working papers shall show the basis and history of this account, including any required approval by a regulatory commission with jurisdiction in the matter or REA in the absence of a commission.

(ii) *Clearing accounts.* The CPA's working papers shall contain an analysis of clearing accounts and evidence that transactions were reviewed for proper allocation between expense and capital accounts.

(3) *Other current assets.* The CPA shall prepare working papers showing the results of a review of the nature and composition of each major account included in this category.

(j) *Capital and equity accounts*—(1) *Capital stock.* For privately owned companies, the CPA shall prepare analyses of the stock transactions during the period and provide documentation showing that:

(i) Subsidiary records were tested and reconciled to the general ledger control account.

(ii) Authorization and issuances or redemptions of capital stock were properly approved by the board of directors, stockholders, and regulatory commissions.

(iii) Transactions were made in accordance with the appropriate provisions of the articles of incorporation, the bylaws, and provisions of the REA loan documents.

(iv) Transactions were recorded in accordance with the uniform system of accounts.

(2) *Memberships.* For cooperative-type organizations, the CPA shall prepare an analysis of the membership transactions during the period, supported by evidence that:

(i) Subsidiary records were tested and reconciled to the general ledger control account.

(ii) Transactions were in accordance with provisions of the articles of incorporation, bylaws, and REA loan documents.

(3) *Patronage capital, retained earnings, margins and other equities.* The CPA shall prepare and include in the working papers an analysis of these and any related reserve accounts, together with evidence that the transactions were vouched. These schedules shall contain evidence that:

(i) The transactions were made in conformity with the provisions of the articles of incorporation, bylaws, REA

loan documents, uniform system of accounts, or orders of the regulatory commissions.

(ii) Payments were tested by tracing to underlying support.

(iii) A determination whether, under the terms of the mortgage, restrictions of retained earning or margins are required and, if so, whether they have been properly recorded.

(k) *Long-term debt.* The CPA shall perform the audit work noted below and provide documentation to evidence this work:

(1) Reconcile long-term debt resulting from REA loans, including accumulated deferred interest, if any, to the most recent statement received from REA. REA automatically mails confirmation schedules of long-term obligation (REA Forms 690 or 691 or RTB Form 12) directly to the CPA selected by the borrower to perform the annual audit. A written request for the confirmation is not necessary. REA does not confirm current interest or accumulated interest accruing subsequent to the date of the latest "Statement of Loan Account and Transactions for Three-Month Period Ending————" (REA Forms 696 or 697 or RTB Form 13).

(2) Confirm other long-term debt directly with the lender.

(3) Examine new mortgages issued or notes canceled during the audit period.

(4) Test accrued interest computations.

(l) *Current and accrued liabilities.* The audit working papers prepared by the CPA shall contain evidence that:

(1) Subsidiary records for each current or accrued liability account were reconciled to the appropriate general ledger control account and include evidence, on a test basis, that the details were traced to disbursement vouchers, invoices and other supporting documentation. The auditor shall also consider direct confirmation with creditors.

(2) Withholdings were analyzed on a test basis and the extent of the verification.

(3) Significant accruals (interest, taxes, etc.) for the period as a whole were analyzed, including the balance of the accrual was tested and important disbursements vouched.

(4) Cash disbursements subsequent to the audit date were reviewed to determine whether the items paid represented liabilities at the audit date.

(5) A search was made for unrecorded liabilities and the results of this search.

(m) *Deferred credits and reserves.* The CPA is required to document the nature and basis of all deferred credits and miscellaneous credits and miscellaneous reserves, together with the extent of the tests made in this area in the audit working papers. If there are deferred credits being held for future disposition, the CPA shall state all facts in the management letter with appropriate recommendations.

(n) *Representation.* (1) The CPA shall document work performed in reviewing for contingencies. Acceptable evidence includes notes of discussions with management, their general counsel and an examination of the board minutes.

(2) A representation letter (SAS No. 19, *Client Representations*) shall be obtained from the borrower's management, and a representation letter as to contingent liabilities and litigation (SAS No. 12, *Inquiry of a Client's Lawyer Concerning Litigations, Claims and Assessments*) shall be obtained from the borrower's attorney.

(o) *Revenues.* (1) The CPA's working papers shall contain an analysis of year-to-year changes in the revenue accounts, together with evidence of a review of significant variations in the current results as compared to the corresponding period in the previous year.

(2) The CPA's working papers shall contain evidence of a selected test of operating revenues from source document through each step of the development of the revenue entry to the final postings in the general ledger. In this connection there shall be evidence that the application of the approved rates, the mathematical accuracy of the billings, and the accounting classification were tested.

(3) The CPA shall determine whether all interest income is being properly accrued and accounted for and document tests performed.

(p) *Expenses.* (1) It is expected that the working papers in this area will emphasize the review and test of internal control and related accounting procedures, particularly the review made to insure that expenses have been properly segregated as to operating and nonoperating expenses.

(2) The CPA's working papers shall contain a comparative analysis of expense accounts supported by evidence that:

(i) All unusual fluctuations were satisfactorily explained.

(ii) Analyses were made of selected accounts to assure proper classification and support for the charges.

(3) Procedures for paying and distributing the costs of payroll for a selected period shall be tested by the CPA. Documentation of payrolls selected for detail testing shall be prepared by the CPA to show:

(i) The extent of mathematical tests and review of supporting documents for pay rates and withholdings.

(ii) A review of the borrower's procedures in distributing payroll costs to capital and expense accounts.

(q) *Related party transactions.* The CPA shall document how he or she has complied with SAS No. 45, *Omnibus Statement on Auditing Standards—1983* (Related Parties). Supporting workpapers shall detail procedures applied and conclusions reached.

(r) *Subsequent events.* In accordance with SAS No. 1, Section 560, *Subsequent Events*, CPAs are responsible for collecting evidential matter pertaining to events between the audit date and the report date (normally the last day of field work). Documentation shall detail: (1) Procedures used to identify subsequent events and (2) the effect of subsequent events on financial statements.

Appendix A—Sample Audit Report for Electric Distribution Cooperatives

Appendix A is an example of a short-form audit report, financial statements and accompanying notes for an electric distribution cooperatives.

The sample audit report is intended as a guide only and, while it is recommended that the format be followed, each audit report should be prepared to adequately cover the circumstances. To the extent possible, it should be used as a guide in preparing audit reports for other types of electric borrowers. For power supply borrowers and for distribution borrowers with production or transmission plant, the same general format should be followed. However, the Statement of Revenue and Patronage Capital must be enlarged to show separate totals for operation expenses and maintenance expenses for each class of production plant and for transmission plant.

March 2, 1984.

The Board of Directors, Center County Electric Cooperative:

We have examined the balance sheets of the Center County Electric Cooperative as of December 31, 19x3 and 19x2, and the related statements of revenue and patronage capital, and of changes in financial position for the years then ended. Our examinations were made in accordance with generally accepted auditing standards and, accordingly, included such tests of the accounting records an such other auditing procedures as we considered necessary in the circumstances.

In our opinion, the financial statements referred to above present fairly the financial position of the Center County Electric Cooperative as of December 31, 19x3 and 19x2, and the results of its operations and the changes in its financial position for the years then ended, in conformity with generally accepted accounting principles applied on a consistent basis.

Certified Public Accountants.

CENTER COUNTY ELECTRIC COOPERATIVE BALANCE SHEET—DECEMBER 31, 19×3 AND 19×2

[Assets (note 1 and 2)]

	19×3	19×2
Electric Plant: (Note 3)		
In Service—at cost	$9,524,646	$9,365,264
Construction work in progress	407,943	317,166
Subtotal	9,932,589	9,682,430
Less: Allowances for depreciation and amortization	3,117,629	2,917,295
Subtotal	6,814,960	6,765,135
Other Assets and investments (at cost):		
Nonutility property	20,227	20,227
Investments in Associated Organizations: (Note 4)	391,258	292,798
Subtotal	411,485	313,025
Current Assets:		
Cash—General funds	37,350	51,544
Cash—Construction funds	10,034	20,193
Accounts Receivable (less provision for doubtful accounts of $2,207 in 19×3 and $1,933 in 19×2)	36,527	35,255
Materials and supplies (at average cost)	83,652	80,882
Other current and accrued assets	8,613	8,692
Subtotal	176,176	196,566
Deferred charges (Note 5):	5,666	1,762
Total	7,408,287	7,276,488

The accompanying notes are an integral part of this statement.

CENTER COUNTY ELECTRIC COOPERATIVE BALANCE SHEET—DECEMBER 31, 19X3 AND 19X2

[Equities and liabilities (Note 1)]

	19X3	19X2
Equities:		
Memberships	$60,145	$59,440
Patronage capital (Note 6)	1,761,798	1,526,833
Other equities (Note 7)	53,647	35,900
Subtotal	1,875,590	1,622,173
Long-Term Debt:		
REA Mortgage notes less current maturities (Note 8)	5,249,115	5,396,385
Current Liabilities:		
Current maturities of long-term debt	145,000	140,000
Accounts payable	70,775	48,673
Consumer deposits	32,660	33,085
Accrued taxes	10,958	19,146
Accrued pension costs (Note 9)	5,900	4,750
Other current and accrued liabilities	7,285	1,711
Subtotal	271,678	247,365
Deferred Credits (Note 10)	11,904	10,565
Contingent liabilities (Note 11)		
Subtotal	7,408,287	7,276,488

CENTER COUNTY ELECTRIC COOPERATIVE STATEMENT OF REVENUE AND PATRONAGE CAPITAL

[For the years ended December 31]

	19X3	9X2
Operating revenues	$1,719,467	$1,605,690
Operating Expenses:		
Cost of power	587,729	625,411
Distribution—Operation	111,058	121,682
Distribution—Maintenance	156,622	162,740
Consumer accounts	76,675	72,927
Sales	38,378	40,755
Administrative and general	94,682	87,058
Depredation and amortization	268,389	279,776
Taxes	34,920	34,438
Interests on long-term debt	113,713	115,082
Subtotal	1,504,166	1,559,869
Operating margins before capital credits	215,301	45,821
G&T and other captial credits	14,460	17,500
Net operating margins	229,761	63,321
Nonoperating Margins:		
Interest Income	24,289	18,802
Other nonoperating income	1,200	1,200
Subtotal	25,489	20,002
Net margins for period	255,250	83,323
Patronage capital—Beginning of year	1,526,833	1,469,125
	1,782,083	1,552,448
Retirement of capital credits	20,285	25,615
Patronage Capital—End of year	1,761,798	1,526,833

The accompanying notes are an integral part of this statement.

CENTER COUNTY ELECTRIC COOPERATIVE STATEMENT OF CHANGES IN FINANCIAL POSITION

[For the years ended December 31]

	19X3	19X2
Funds Were Provided By:		
Net margins before provision for depreciation and amortization of (19X3 $290,562; 19X2 $281,033)	$545,812	$364,356
G&T and other capital credits (non-cash)	(14,460)	(17,500)
Membership fees	705	600
Advances from REA	174,976	278,500
Retired capital credits—gain	1,200	
Material returned to stock from retirements	10,014	8,473
Increase in deferred credits	1,339	576
Decrease in working capital	39,703	2,798
	759,289	637,803
Funds Were Used For:		
Extension and replacement of plant	289,787	242,584
Payments on long-term debt to REA including portion maturing within one year	322,387	289,667
Increase in investments (net)—(excluding capital credits assigned)	96,932	57,868
Increase in deferred charges	3,904	2,640
Plant removal costs	25,994	19,429
Retirement of patronage capital	20,285	25,615
	759,289	637,803
Change in Components of Working Capital:		
Increase (decrease) in current assets:		
Cash—General funds	(14,194)	(8,133)
Cash—Construction funds	(10,159)	6,799
Accounts receivable	1,272	(2,143)

CENTER COUNTY ELECTRIC COOPERATIVE STATEMENT OF CHANGES IN FINANCIAL POSITION—Continued

[For the years ended December 31]

	19X3	19X2
Material and supplies	2,770	1,872
Other current and accrued assets	(79)	112
	(20,390)	(1,493)
(Increase) decrease in current liabilities:		
Accounts Payable	(22,102)	1,987
Consumer Deposits	425	(83)
Accrued Taxes	8,188	794
Accrued Pension Costs	(250)	(300)
Other Current Liabilities	(5,574)	(3,703)
	(19,313)	(1,305)
Net decrease in working capital	(39,703)	(2,798)

The accompanying notes are an integral part of this statement.

Center County Electric Cooperative Notes to Financial Statements

[December 31, 19X3 and December 31, 19x2]

1. Summary of Significant Accounting Policies:

Present a description of the reporting entity's significant accounting policies in accordance with Accounting Principles Board Opinion No. 22, *Disclosure of Accounting Policies.*

Disclosure of accounting policies should identify and describe the accounting principles followed by the borrower and the methods of applying these principles that materially affect the determination of financial position, changes in financial position and results of operations.

Disclosures of accounting policies do not have to be duplicated in this section if presented elsewhere as an integral part of the financial statements.

2. Assets Pledged:

All assets are pledged as security for long-term debt to REA.

3. Electric Plant and Depreciation Procedures:

Listed below are the major classes of the electric plant as of December 31, 19X3, and 19X2:

	19X3	19X2
Intangible plant	$2,194	$2,194
Distribution plant	9,011,036	8,873,957
General plant	511,416	489,113
Electric plant in service	9,524,646	9,365,264
Construction work in progress	407,943	317,166
	9,932,589	9,682,430

Provisions has been made for depreciation of distribution plant at a straight-line composite rate of 2.86 percent per annum.

General Plant depreciation rates have been applied on a straight-line basis and are as follows:

	Percent
Structures and improvement	2.5
Office furniture	6.0
Transportation equipment	14.0
Power operated equipment	12.0

	Percent
Other general plant	4.0
Communications equipment	6.0

4. Investments in Associated Organizations:

Investments in associated organizations consisted of the following at December 31, 19X3 and 19X2:

	19X3	19X2
Capital term certificates of the National Rural Utilities Cooperative Finance Corporation (NRUCFC)	$385,193	$288,261
Patronage capital credits invested by NRUCFC	5,065	3,537
Other	1,000	1,000
	391,258	292,798

The Cooperative is obligated to purchase additional CTCs of approximately $76,100 in October 19X4 and a similar amount in October 19X5.

5. Deferred Charges:

Following is a summary of amounts recorded as deferred charges as of December 31, 19X3 and 19X2:

	19X3	19X2
Preliminary surveys 19X4–X5 work plan	$3,486	0
Deferred interest	2,180	$1,762
	5,666	1,762

6. Patronage Capital:

At December 31, 19X3 and 19X2, patronage capital consisted of:

	19X3	19X2
Assignable	$255,250	$83,323
Assigned	1,526,833	1,469,125
	1,782,083	1,552,448
Less: Retirements	20,285	25,615
	1,761,798	1,526,833

7. Other Equities:

At December 31, 19X3 and 19X2, other equities consisted of:

	19X3	19X2
Retired capital credits—Gain	$36,190	$34,990
Donated capital	17,457	910
	53,647	35,900

8. Mortgage Notes—REA:

Long-term debt is represented by mortgage notes payable to the United States of America. Following is a summary of outstanding long-term debt as of December 31, 19X3 and 19X2:

	19X3	19X2
2 Percent notes due March 31, 19X4	$1,057,155	$1,098,700
2 Percent notes due December 31, 19X6	2,485,927	2,502,370
5 Percent notes due December 31, 19X6	1,651,033	1,935,315
Less: Current maturities	(145,000)	(140,000)
	5,249,115	5,396,385

Unadvanced loan funds of $285,600 are available to the cooperative on loan commitments from REA.

Principal and interest installments on the above notes are due quarterly in equal amounts of $99,600. As of December 31, 19X3, annual maturities of long-term debt outstanding for the next five years are as follows:

19X4	$145,000
19X5	150,000
19X6	151,500
19X7	154,000
19X8	155,000

Advance payments of $252,300 may be applied to the installments.

9. Pension Plan:

Substantially all of the employees of the Cooperative are covered by the ABC Retirement and Security Program. The total pension expense for 19X3 was $22,400 and 19X2 was $20,400, including $8,680 and $8,630 respectively of past service costs being amortized over 10 years. These past service costs will be fully amortized in 19X8. The amount of accrued pension expense for the year is funded by the Cooperative in quarterly annual contributions to the pension plan.

A comparison of accumulated plan benefits and plan net assets as of December 31, 19X3 and 19X2 is presented below:

[In thousands of dollars]

	19X3	19X2
Actual present value of accumulated plan benefits:		
Vested	$2,563	$2,289
Nonvested	1,398	1,055
	3,961	3,344
Estimated net assets available for benefits	5,731	5,317

The assumed rate of return used in determining the actual present value of accumulated plan benefit was 7½ of in 19X3 and 19X2.

10. Deferred Credits:

Following is a summary of the amounts recorded as deferred credits as of December 31, 19X3 and 19X2.

	19X3	19X2
Customer energy prepayments	$6,694	$3,065
Inventory adjustment	5,210	7,500
	11,904	10,565

11. Litigation:

The cooperative is defendant in an action in which the plaintiff claims damages totaling $200,000 for personal injuries sustained. The action has been dismissed by the District Court, but is on appeal before the State Supreme Court. Counsel is of the opinion that no liability will be incurred by the cooperative as a result of this action.

Appendix B—Sample Audit for Class A or B Commercial Telephone Companies

This sample audit report is intended as a guide. Audits will vary in each case, and while it is recommended that the format be followed, each audit report should be prepared to adequately cover the circumstances.

This short-form audit report has been prepared to illustrate the type of audit report and financial statements considered appropriate for commercial telephone companies financed by REA. Terminology relating to cooperative telephone companies is illustrated in Appendix A.

March 2, 19X4

Accountants' Report

The Board of Directors, Center Telephone Company:

We have examined the balance sheets of the Center Telephone Company as of December 31, 19X3 and 19X2, and the related statements of income and retained earnings, and changes in financial position for the years then ended. Our examinations were made in accordance with generally accepted auditing standards, and, accordingly included such tests of the accounting records and such other auditing procedures as we considered necessary in the circumstances.

In our opinion, the financial statements referred to above present fairly the financial position of the Center Telephone Company as of December 31, 19X3 and 19X2, and the results of its operations and the changes in financial position for the years then ended, in conformity with generally accepted accounting principles applied on a consistent basis.

Certified Public Accountants.

CENTER TELEPHONE COMPANY BALANCE SHEET—DECEMBER 31, 19X3 AND 19X2

[Assets (Notes 1 and 2)]

	19X3	19X2
Property, Plant and Equipment (Note 3):		
In service	$7,401,300	$6,850,553
Under construction	67,626	199,092
Acquisition adjustment (Note 4)	176,380	176,380
	7,645,306	7,026,025
Less: Accumulated provision for depreciation	1,760,587	1,504,255
	5,884,719	5,521,770
Miscellaneous physical property (Note 5):		
Net CATV plant	413,511	407,086
Net deregulated customer premises equipment	103,618	0
	6,401,848	5,928,856
Current Assets:		
Cash—Construction funds	21,000	18,000
Cash—General funds	128,300	140,083
Notes Receivable	2,500	3,000
Due from customers and agents (less reserve of $11,597 in 19X3 and $1,490 in 19X2)	139,642	122,623
Materials and supplies (at average cost)	103,713	73,964
Other current assets	1,357	10,131
	396,512	367,801

CENTER TELEPHONE COMPANY BALANCE SHEET—DECEMBER 31, 19X3 AND 19X2—Continued

[Assets (Notes 1 and 2)]

	19X3	19X2
Prepaid Expenses and Deferred Charges:		
Prepayments (Note 6)	49,185	62,201
Extraordinary retirements (Note 7)	40,000	45,000
	89,185	107,201
	6,887,545	6,403,858

The accompanying notes are an integral part of this statement.

CENTER TELEPHONE COMPANY BALANCE SHEET—DECEMBER 31, 19X3 AND 19X2

[Equities and liabilities]

	19X3	19X2
Capital Stock and Retained Earnings:		
Capital stock—Common $10 par value—300,000 shares authorized 102,600 shares outstanding 19X3 and 19X2	$1,026,000	$1,026,000
Retained earnings (Note 8)	582,146	405,626
	1,608,146	1,431,626
Long-Term Debt:		
REA Mortgage notes (Note 8)	4,592,658	4,128,106
Current Liabilities:		
Current portion of long-term debt (Note 8)	146,646	145,998
Notes payable	61,600	70,400
Accounts payable	123,689	290,484
Customers deposits	11,878	4,940
Advance billings and payments	2,137	2,243
Accrued taxes	242,076	224,566
Accrued pension costs (Note 9)	2,500	2,000
Other current liabilities	6,000	7,079
	596,526	747,710
Deferred Credits:		
Deferred investment tax credit (Note 10)	90,215	96,416
	6,887,545	6,403,858

The accompanying notes are an integral part of this statement.

CENTER TELEPHONE COMPANY, STATEMENT OF INCOME AND RETAINED EARNINGS

[For the years ended December 31]

	19X3	19X2
Operating Revenues:		
Local service	$961,864	$882,205
Toll service	897,300	755,073
Miscellaneous	144,435	147,100
Less: Uncollectible revenues	(24,000)	(24,500)
	1,979,599	1,759,878
Operating Expenses:		
Maintenance	339,839	284,226
Traffic	257,853	206,427
Commercial	78,965	70,149
General office salaries and expenses	153,899	142,750
Other operating expenses	98,027	80,231
Depreciation (Note 3)	332,044	309,564
Amortization	17,638	13,144
Investment credits—Net	6,201	1,640

CENTER TELEPHONE COMPANY, STATEMENT OF INCOME AND RETAINED EARNINGS—Continued

[For the years ended December 31]

	19X3	19X2
Federal income taxes—Operating	191,411	200,155
Other operating taxes	225,013	204,230
	1,700,890	1,492,576
Operating income	278,709	267,302
Other Income and (Deductions):		
Income from miscellaneous physical property—Net (Note 5)	19,902	10,593
Income available for fixed charges	298,611	277,895
Fixed Charges:		
Interest on long-term debt	88,432	85,854
Interest charged to construction—Credit	(2,251)	(1,516)
	86,181	84,338
Net income for period	212,430	193,557
Retained earnings—January 1, 19X2 and 19X1	405,626	235,153
Dividends declared	(35,910)	(23,084)
Retained earnings—December 31, 19X3 and 19X2	582,146	405,626
Earnings per share of common stock—Average	2.07	1.89

The accompanying notes are an integral part of this statement.

CENTER TELEPHONE COMPANY STATEMENT OF CHANGES IN FINANCIAL POSITION

[For the year ending December 31]

	19x3	19x2
Funds Were Provided by:		
Net income before depreciation (19x3–$367,044 and 19x2–$326,342)	$579,474	$519,899
Advances from REA	505,849	31,340
Decrease (Increase) in investments	99,575	(78,965
Materials returned to stock	50,000	54,007
	1,234,898	526,281
Funds Were Used For:		
Telephone plant additions and replacements	759,100	585,097
Miscellaneous physical property additions and replacements	105,159	0
Payments and reclassification of long-term debt due within one year	146,649	145,998
Plant removal costs	20,000	18,437
Increase (decrease) in deferred charges	(18,016)	36,464
Decrease (Increase) in deferred credits	6,201	(1,640)
Dividends on common stock	35,910	23,084
Increase (decrease) in working capital	179,895	(281,159)
	1,234,898	526,281
Analysis of Increase (Decrease) in Working Capital:		
Increase (decrease) in current assets:		
Cash—Construction funds	3,000	(18,408)
Cash—General funds	(11,783)	4,686
Notes Receivable	(500)	(781)
Due from customers and agents	17,091	26,569
Materials and supplies	29,749	(13,707)
Other current assets	(8,774)	46,477
	28,711	44,856

CENTER TELEPHONE COMPANY STATEMENT OF CHANGES IN FINANCIAL POSITION—Continued

[For the year ending December 31]

	19x3	19x2
Increase (decrease) in current liabilities:		
Current portion of long-term debt	648	104
Notes payable	(8,800)	(4,036)
Accounts payable	(166,795)	(2,325)
Customer Deposits	6,938	(278,727)
Advance billings and payments	(106)	(228)
Accrued taxes	17,510	37,742
Accrued pension costs	500	1,077
Other current liabilities	(1,079)	14,954
	(151,184)	326,015
Increase (decrease) in working capital	179,895	(281,159)

The accompanying notes are an integral part of this statement.

Center Telephone Company Notes to Financial Statements

[December 31, 19X3 and December 31, 19X2]

1. Summary of Significant Accounting Policies:

Include a brief description of the reporting entity's significant accounting policies in accordance with Accounting Principles Board Opinion No. 22, *Disclosure of Accounting Policies.*

Disclosure of accounting policies should identify and describe the accounting principles followed by the borrower and the methods of applying those principles that materially affect the determination of financial position, changes in financial position and results of operations.

Disclosures of accounting policies do not have to be duplicated in this section if presented elsewhere as an integral part of the financial statements.

2. Assets Pledged:

All assets are pledged as security for the long-term debt to REA.

3. Investment in Telephone Plant:

Telephone plant in service and under construction is stated at cost. The company provides for depreciation on a straight-line basis at annual rates which will amortize the depreciable property over its estimated useful life. Listed below are the major classes of the telephone plant as of December 31, 19X3 and 19X2:

	19X3	19X2
Organization	$4,507	4,507
Land	56,070	56,070
Buildings	560,200	495,760
Central office equipment	2,570,364	2,13,581
Toll and subscriber carriers	500,798	390,920
Station apparatus	230,196	197,350
Station connections	200,948	153,878
Poles, cables, wire	2,408,895	2,082,760
Furniture and office equipment	57,045	45,188
Tools and other work equipment	200,327	190,287
Telephone plant in service unclassified	611,950	900,252
Telephone plant in service	7,401,300	6,650,553

General plant depreciation rates have been applied on a straight-line basis and are as follows:

	Percent
Buildings	4
Central Office Equipment	4
Toll and Subscriber Carriers	10
Station Apparatus	13.3
Station Connections	5
Outside Plant—Aerial and Buried Cable	4-5
Outside Plant—Pole Lines and Aerial Wire	25
Office Furniture	10
Vehicles	25
Work Equipment	16

4. Telephone Plant Acquisition Adjustment:

This adjustment represents the difference between the amount paid for the telephone plant plus associated expenses and the original cost of the plant less the associated depreciation. The company is amortizing the adjustment over a 19½ year period in accordance with the Public Utility Commission. Annual amortization amounts to $9,000.

5. Miscellaneous Physical Property:

	19X3	19X2
CATV plant in service	$430,440	$420,940
CATV plant under construction	9,051	6,500
Total CATV plant	439,491	427,440
Less accumulated depreciation	25,980	20,354
Net CATV plant	413,511	407,086

CATV plant in service and under construction is stated at cost. The company provides for depreciation on a straight-line basis at annual rates which will amortize the depreciable property over its estimated useful life.

	19X3	19X2
Deregulated customer premises equipment—leased	$109,699	0
Less: Accumulated provisions for depreciation	6,081	0
	103,618	0

Deregulated customer premises equipment was reclassified as miscellaneous physical property as of January 1, 1983. Deregulated CPE is stated at cost. The company provides for depreciation on a straight-line basis at an annual rate of depreciation which will amortize the cost of the equipment over its estimated useful life.

Following is a summary of net income from miscellaneous physical property for the year ending December 31, 19X3:

	Deregulated		
	CATV	CPE	Total
Income from operations	$32,425	$9,151	$41,576
Expenses	18,834	2,840	21,674
	13,591	6,311	19,902

6. Prepaid Expenses:

Following is a summary of the amounts recorded as prepaid items as of December 31, 19X3 and 19X2:

	19X3	19X2
Prepaid taxes	$10,000	$20,000
Prepaid insurance	3,000	3,000
Prepaid rent	36,185	39,201
	49,185	62,201

7. Deferred Charges:

The balance consists of the unamortized portion of the unprovided for loss in service value of plant retired.

Description	Data	Original balance net of income-tax savings	Unamortized Balance	
			19X3	19X2
Aerial Plant	1/1/X1	50,000	40,000	45,000

The Public Utilities Commission granted the company permission to amortize this loss over a ten year period net of income tax savings of $10,542.

8. Mortgage Notes:

Long-term debt is represented by mortgage notes payable to the United States of America. Following is a summary of outstanding long-term debt:

	19X3	19X2
5 percent notes due December 31, 19X0	$4446,012	$4,274,104
Less: Current maturities	146,846	145,998
	4,592,658	4,128,106

As of December 31, 19X3, there were no unadvanced loan funds.

Principal and interest installments on the above notes are due quarterly in equal amounts of $63,200. The maturities of long-term debt for each of the five years succeeding the balance sheet date is as follows:

19X4	$146,849
19X5	153,839
19X6	155,743
19X7	143,000
19X8	139,976

The long-term debt agreements contain restrictions on the payment of dividends or redemption of capital stock. The terms of the mortgage agreement require the maintenance of defined amounts of members' equity and working capital after payment of dividends. Under these provisions approximately $293,688 of retained earnings was available for payment of dividends at December 31, 19X3.

9. Pension Plan:

The Corporation has a defined pension plan in effect for all employees. All accrued pension costs are funded through participation in a retirement program with the ZYX Reserve Insurance Company. The fund covers all vested benefits under the plan. The expense for the year ended 19X3 was $12,000 as compared to $11,500 for 19X2. The actuarial present value of accumulated benefits and the net assets available for those benefits are as follows:

[In thousands of dollars]

	19X3	19X2
Actuarial Present Value of Accumulated Plan Benefits:		
Vested	$1,340	$1,290
Nonvested	930	875
Total	2,270	2,065
Net assets available for benefits	3,455	3,200

The assumed rate of return used in determining the actuarial present value of accumulated plan benefits was 6 percent for both 19X3 and 19X2. A plan amendment effective July 1, 19X2, refunded approximately $1,000 to current employees representing their contributions to the plan. The refund had no effect on the employees' pension benefits and did not materially affect the actuarial present value of vested accumulated plan benefits. Beginning in 19X4, this amendment is expected to increase annual pension costs by approximately $300.

10. Deferred Credits:

The company follows the practice of recording investment tax credit as a deferred income, to be amortized over the life of the assets providing the credit as required by the Public Service Commission. Accordingly, Federal income tax expense at December 31, 19X3 was reduced $7,400 by the investment tax credit amortization.

Appendix C—Sample Management Letter (Electric or Telephone)

REA requires that CPAs auditing REA borrowers provide a management letter in accordance with § 1789.32.

REA requires that this letter bear the same date as the accountant's report and be addressed to the board of directors. The CPA is required to sign both the management letter and the accountant's report.

March 2, 19X4.

Board of Directors, Electric or Telephone Cooperative, Inc.:

We have examined the financial statements of (company) for the year ended December 31, 19X3, and have issued our report thereon dated March 2, 19X4. As part of our examination, we made a study and evaluation of the company's system of internal accounting control to the extent we considered necessary to evaluate the system as required by generally accepted auditing standards and specific REA audit requirements. The purposes of our study and evaluation were to determine the nature, timing and extent of the auditing procedures necessary for expressing an opinion on the company's separate management letter required by REA. Our study was more limited than would be necessary to express an opinion on the system of internal accounting control taken as a whole.

The management of (company) is responsible for establishing and maintaining a system of internal accounting control. In fulfilling this responsibility, estimates and judgments by management are required to assess the expected benefits and related costs of control procedures. The objectives of

a system are to provide management with reasonable, but not absolute, assurance that assets are safeguarded against loss from unauthorized use or disposition, and that transactions are executed in accordance with management's authorization and recorded properly to permit the preparation of financial statements in accordance with generally accepted accounting principles.

Because of inherent limitations in any system of internal accounting control, errors or irregularities may nevertheless occur and not be detected. Also, projection of any evaluation of the system to future periods is subject to the risk that procedures may become inadequate because of changes in conditions or that the degree of compliance with the procedures may deteriorate.

Our study and evaluation made for the limited purposes described in the first paragraph would not necessarily disclose all material weaknesses in the system. Accordingly, we do not express an opinion on the system of internal accounting control of (company) taken as a whole. However, our study and evaluation disclosed no condition that we believed to be a material weakness.

Our comments on specific financial and accounting matters as required by REA and other comments and recommendations developed during our examination, which do not represent material internal control weaknesses, are detailed below.

In instances where the study and evaluation of internal control discloses material weaknesses (as defined in Statement on Auditing Standards No. 20, *Required Communication of Material Weaknesses in Internal Accounting Control*, the last sentence of the fourth paragraph and the fifth paragraph should be modified as follows:

However, our study and evaluation disclosed conditions that we believe result in more than a relatively low risk that errors or irregularities in amounts that would be material in relation to the financial statements of (company) may occur and not be detected within a timely period. These conditions were considered in determining the nature, timing and extent of the audit tests to be applied in our examination of the 19X3 financial statements, and this report does not affect our report on these financial statements dated March 2, 19X4.

These material weakness as well as comments on specific financial and accounting matters as required by REA and other comments and recommendations developed during our examination, which do not represent material weaknesses, are detailed below:

Comments

Material Weaknesses in Internal Accounting Control (if applicable).

Weaknesses in Internal Accounting Control not considered Material.

Required Comments on Specific Financial and Accounting Matters (as detailed in § 17XX.XX).

Internal Control (additional information required by REA).

Accounting and Records.

Material Control.

Compliance with Loan Documents.

Reports to REA.

Service Contracts.

Deposits.

Income Tax Status.

Related Party Transactions.

Sale of Plant.

Depreciation Rates.

Other Comments and Recommendations.

This letter supplements the information included in the financial statements and notes. It is intended solely for the use of management, the Rural Electrification Administration, and supplemental lenders and should not be used for any other purpose.

In accordance with the terms of our engagement, we are enclosing copies of the report, management letter, and adjusting/reclassification entries for each member of the Board, the Manager, and other required distribution. Two copies of the report, management letter and entries should be transmitted to the REA and one copy transmitted to supplemental lender, where applicable.

Certified Public Accountants.

Dated: October 15, 1984.

Jack Van Mark,

Acting Administrator.

[FR Doc. 85-1225 Filed 1-22-85; 8:45 am]

BILLING CODE 3410-15-M

federal register

Wednesday
January 23, 1985

Part IV

Department of Energy

Office of Civilian Radioactive Waste Management

Nuclear Waste Policy Act of 1982; Public Hearings on the Draft Environmental Assessments for Proposed Site Nominations

DEPARTMENT OF ENERGY

Office of Civilian Radioactive Waste Management; Nuclear Waste Policy Act of 1982; Public Hearings on the Draft Environmental Assessments for Proposed Site Nominations.

AGENCY: Department of Energy (DOE).

ACTION: Notice of public hearings on draft environmental assessments (EAs).

SUMMARY: The DOE has scheduled public hearings to receive oral comments from the public on the draft EAs prepared for nine potentially acceptable nuclear waste repository sties. These nine draft EAs were issued for public review and comment on December 20, 1984 (See 49 FR 49540).

FOR INFORMATION YOU MAY CONTACT:

1. (a) For the public hearings on the Richton Dome (Mississippi), Cypress Creek Dome (Mississippi), Vacherie Dome (Louisiana), Deaf Smith County (Texas), Swisher County (Texas), Davis Canyon (Utah), and Lavender Canyon (Utah) draft EAs—Jefferson O. Neff, Program, Manager, Salt Repository Project Office, Chicago Operation Office, U.S. Department of Energy, 505 King Avenue, Columbus, OH 43201. Phone: (615) 424–5916.

(b) For the public hearings on the Yucca Mountain (Nevada) draft EA—Donald Vieth, Director, Waste Management Project Office, Nevada Nuclear Waste Storage Investigations, Nevada Operations Office, U.S. Department of Energy, P.O. Box 14100, Las Vegas, Nevada 89109. Phone: (702) 295–3662.

(c) For the public hearings on the Hanford (Washington) draft EA—O. Lee Olson, Project Manager, Basalt Waste Isolation Project, Richland Operations Office, U.S. Department of Energy, P.O. Box 550, Richland, WA 99352. Phone: (509) 376–7334.

2. Gerald J. Parker, Team Leader, Site Evaluation Team, Siting Division, Office of Geologic Repositories, Office of Civilian Radioactive Waste Management, U.S. Department of Energy, Washington, D.C. 20585. Phone: (202) 252–1116.

3. Robert Mussler, Esq., Deputy Assistant General Counsel for Environment, Office of General Counsel, U.S. Department of Energy, Washington, D.C. 20585. Phone: (202) 252–6947.

SUPPLEMENTARY INFORMATION:

I. Public Hearing Locations, Dates, and Times

Public hearings on the draft EAs are scheduled as follows:

DRAFT ENVIRONMENTAL ASSESSMENT HEARINGS

Site(s)—city, and state	Address	Date	Time(s)
Yucca Mountain:			
Amargosa Valley, NV	Amargosa Valley Community Building, Amargosa Farm Road	2/25/85	10–2 a.m.: 6–10 p.m.
Las Vegas, NV	Hacienda Hotel, Madrid Room, 3950 Las Vegas Boulevard—South	2/26/85	10–2 a.m.: 6–10 p.m.
Reno, NV	Jot Travis Student Union, Pine Room, University of Nevada—Reno	2/28/85	10–2 a.m.: 6–10 p.m.
Hanford:			
Richland, WA	Federal Building Auditorium, 825 Jadwin Avenue	3/05/85	2–5 p.m. 7–10 p.m.
Olympia, WA	Department of Social & Health Services, Hearing Room, Office Building #2, Twelfth and Franklin Streets.	3/07/85	2–5 p.m. 7–10 p.m.
Lavender Canyon & Davis Canyon:			
Monticello, UT	Monticello High School, 164 South Second Street—West	2/19/85	4–9 p.m.
Moab, UT	Helen M. Knight Elementary School, West Fourth North Street	2/20/85	4–9 p.m.
Salt Lake City, UT	Hotel Utah, South Temple and Main Streets	2/22/85	2–9 p.m.
Deaf Smith County & Swisher County:			
Tulia, TX	Tulia High School, 501 N.E. Fourth Street	2/26/85	4–9 p.m.
Hereford, TX	Hereford High School, 701 Union Street	2/28/85	4–9 p.m.
Austin, TX	Austin Hilton Inn, I–35 at Highland Mall, 6000 Middle Fiskville Road	3/01/85	2–9 p.m.
Richton Dome & Cypress Creek Dome:			
Jackson, MS	Holiday Inn—North, 5075 I–55 North (Briarwood Exit)	2/21/85	2–9 p.m.
Richton, MS	Richton High School, Auditorium, 701 Elm Street	2/22/85	4–9 p.m.
Gulfport, MS	Gulf Coast Community College Auditorium, Jefferson Davis Campus, 2226 Switzer Road	2/23/85	1–6 p.m.
Vacherie Dome:			
Minden, LA	Civic Center Auditorium, 520 Broadway Street	2/25/85	4–9 p.m.
Baton Rouge, LA	Prince Murat Hotel, 1480 Nicholson Drive	2/26/85	2–9 p.m.

II. Presentation Procedure

Any person or representative of a group may submit a written request for an opportunity to make an oral presentation at a public hearing. Such requests must be received no later than ten days before the scheduled hearing. Requests should be sent to the appropriate hearing contact at the address given above. Anyone making a request should provide a phone number at which he or she may be contacted through the day of the hearing. All written requests for opportunities to present comments shall be acknowledged by DOE.

At the hearing, those who have registered in advance will be heard first or at times reserved for them. Anyone present at the hearing who would like to speak but did not preregister may request an opportunity to speak. The moderator at the hearing will determine if such requests can be accommodated within the time period scheduled.

Each person scheduled to appear at a specific hearing is requested to bring a written copy of his or her statement for submission to the hearing record.

III. Conduct of Hearings

DOE reserves the right to arrange the schedule of presentations to be heard and to establish additional procedures governing the conduct of the hearing. To ensure that as many interested persons as possible are given the opportunity to present oral comments, the length of each presentation will be limited to no more than 10 minutes, and may be further limited for a particular hearing depending upon the number of persons requesting to be heard.

Questions may be asked only by those conducting each hearing, and there will be no cross-examination of persons presenting statements. Any further procedural rules needed for the proper conduct of the hearing will be announced by the moderator at the start of the hearing.

IV. Written Comments

DOE will consider both oral and written comments received on the draft EAs. The opportunity to provide written comments on the draft EAs is afforded by a public comment period which is scheduled to end on March 20, 1985 (49 FR 49540, December 20, 1984). Written comments should be sent to: Comments—EA, U.S. Department of Energy, Attn: Comments-EA, 1000 Independence Avenue SW.,

Washington, D.C. 20585. The specific EA being addressed in each comment should be clearly identified.

As noted above, written comments on a draft EA may also be submitted at the public hearing.

V. Transcripts

A transcript of each public hearing will be made. Transcript copies will be made available for public inspection at the following locations, at the indicated times Monday through Friday, except Federal holidays and where noted below:

- DOE Public Reading Room, Room 1E–190, Forrestal Building, 1000 Independence Avenue SW., Washington, D.C. 20585, 9:00 a.m. to 4:00 p.m.
- Albuquerque Operations Office, Kirtland Air Force Base, National Atomic Museum Library, Public Reading Room, Albuquerque, New Mexico 87115, (505) 844–8443, 9:00 a.m. to 5:00 p.m.
- Chicago Operations Office, 9800 South Cass Avenue, Argonne, Illinois 60439, 8:00 a.m. to 5:00 p.m.
- Idaho Operations Office, 550 2nd Street, Headquarters 199, Idaho Falls, Idaho 83401, (208) 526–0271, 8:00 a.m. to 5:00 p.m.
- Nevada Operations Office, Public Docket Room 2753 S. Highland, Las Vegas, Nevada 89114, (702) 734–3521, 8:00 a.m. to 4:30 p.m.
- Oak Ridge Operations Office, 200 Administration Road, Room G208, Federal Building, Oak Ridge, Tennessee 37830, (615) 576–1218, 8:00 a.m. to 4:30 p.m.
- Richland Operations Office, Hanford Science Center-Rockwell Hanford Operations, 825 Jadwin Avenue, Federal Building, Richland, Washington 99352, (509) 376–8273, Sunday 1:00 p.m. to 5:00 p.m., Monday through Saturday 9:00 to 5:00 p.m.
- San Francisco Operations Office, 1333 Broadway, Wells Fargo Building, Reading Room, Room 240, Oakland, California 94612, (415) 273–4358, 8:30 a.m. to 4:00 p.m.
- Savannah River Operations Office, 211 York Street NE., Federal Building, Aiken, South Carolina 29801 (803) 725–3267, 8:30 a.m. to 4:00 p.m.
- Minden Nuclear Waste Information Office, 221 Main Street, Minden, LA 71005, (318) 371–0369, 11 a.m.–3 p.m., Mon-Fri.
- Bienville Parish Library, 604 South Maple, Arcadia, LA 71001.
- Webster Parish Library, 521 East and West Streets, Minden, LA 71005.
- Richton Nuclear Information Office, 103 Dogwood, Richton, MS 39476, (601) 788–6948, 8 a.m.–5 p.m., Thurs.–Sat., 5 p.m.–9 p.m., Mon. & Tues.
- Pine Forest Regional Library, Main Street, Richton, MS 39476.
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- Deaf Smith County Library, 211 East Fourth Street, Hereford, TX 79045.
- Nuclear Waste Information Office, 115 East First, Hereford, TX 79045.
- Swisher County Library, Swisher County Memorial Bldg., Tulia, TX 79088.
- Nuclear Waste Information Office, 110 SE., Second, Tulia, TX 79088.
- Randall County Library, 201 16th Street, Canyon, TX 79015.
- Amarillo Public Library, 413 East Fourth Street, P.O. Box 2172, Amarillo, TX 79189.
- Texas Nuclear Waste Programs Office, Sam Houston Office Bldg., Room 204, 200 East 14th Street, Austin, TX 78711.
- Rhodes Memorial Library, 103 SW. 2nd Street, Dimmitt, TX 79027.
- Gabie Betts Burton Memorial Library, 314 South Sully, P.O. Box 783, Clarendon, TX 79226.
- Austin Public Library, 800 Guadalupe Street, P.O. Box 2287, Austin, TX 78768.
- University of Texas Genereal Library, P.O. Box P, Austin, TX 78712.
- Moab Nuclear Waste Information Office, 471 S. Main St., #3, Moab, UT 84532, (801) 259–8727, 8 a.m.–2 p.m., Tues.–Fri.
- Monticello Nuclear Waste Information Office, San Juan County Courthouse, 117 S. Main St., Rm. 12, Monticello, UT 84535, (801) 587–2231, Ext. 28, 8:00 a.m.–Noon, Mon.–Fri.
- Grand County Library, 25 South First Street, East, Moab, UT 84532.
- Grand County High School Library, 300 South 100 East, Moab, UT 84532.
- San Juan County Library, 266 North Main Street, Monticello, UT 84535.
- Monticello High School Library, Media Center, 164 South 2nd West, Monticello, UT 84535.
- Mesa County Public Library, 530 Grand Avenue, Grand Junction, CO 81501.
- Salt Lake City Public Library, 205 East 5th Street South, Salt Lake City, UT 84111.
- University of Utah, Marriott Library, Salt Lake City, UT 84112.

Any person may purchase a copy of the transcript of the hearing from the reporter, so identified by the moderator.

Issued in Washington, D.C. January 16, 1985.

Ben C. Rusche,

Office of Civilian Radioactive Waste Management.

[FR Doc. 85–1677 Filed 1–17–85; 5:01 p.m.]

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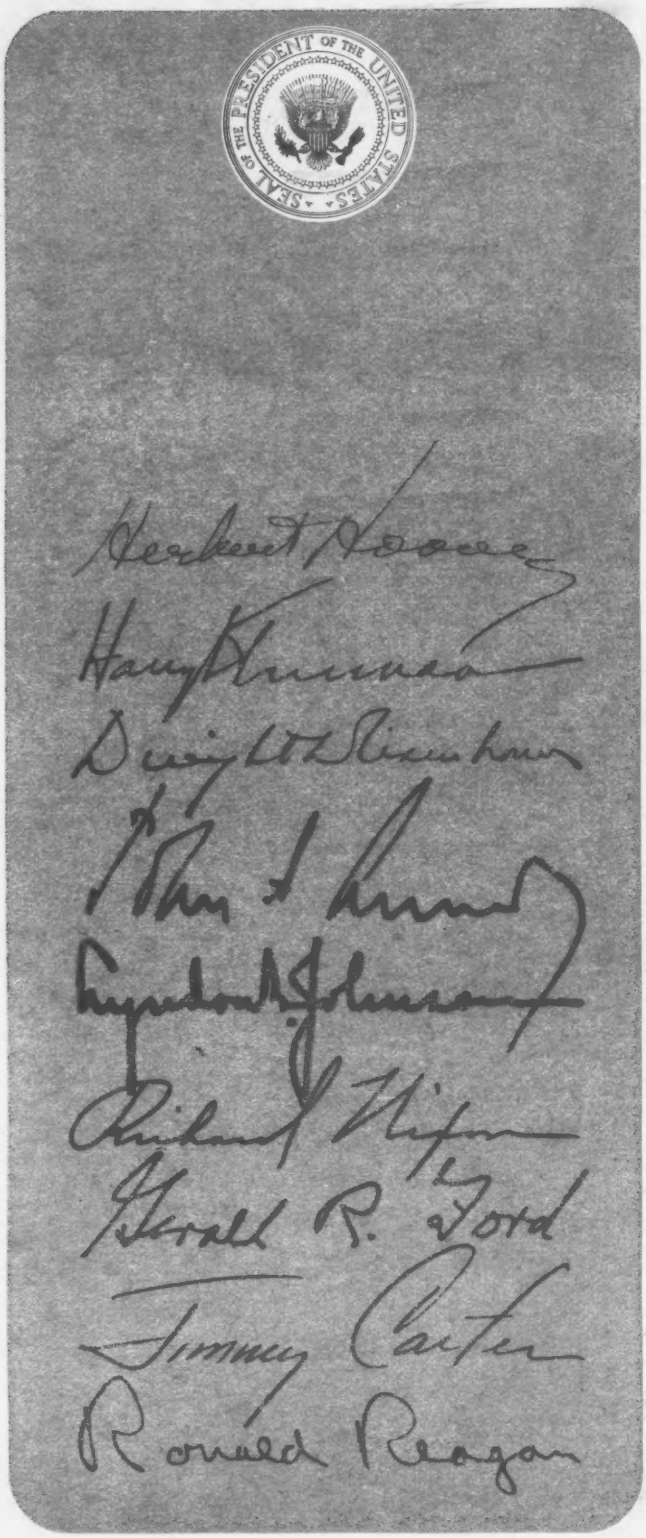

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